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=> fil cancer

FILE 'CANCERLIT' ENTERED AT 08:52:03 ON 04 FEB 1999

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=> d his l51-


     (FILE 'CANCERLIT' ENTERED AT 08:23:18 ON 04 FEB 1999)
                E GASIT A/AU
                E GAZIT A/AU
L51          80 S E3
                E LEVITZKI A/AU
L52          61 S E3
                E CAVENEE W/AU
L53         157 S E3,E5
                E NAGANE M/AU
L54          21 S E3
                E HUANG H/AU
L55         121 S E3,E10,E11
L56           0 S L12
L57          37 S AG1478 OR AG 1478 OR TRYPHOSTIN? (L) 1478
L58           4 S L51-L55 AND L57
L59       31718 S L19 OR CISPLATIN/CT,CN OR VINCRISTINE/CT,CN OR PACLITAXEL/CT,
L60           1 S L57 AND L59
L61           4 S L58,L60
L62       12512 S APOPTOSIS+NT/CT
L63           6 S L57 AND L62
L64           7 S (CELL DEATH+NT OR CELL SURVIVAL+NT)/CT AND L57
                E (RECEPTORS, EPIDERMAL GROWTH FACTOR-UROGASTRONE+NT)/CT
L65        5398 S (RECEPTORS, EPIDERMAL GROWTH FACTOR-UROGASTRONE+NT)/CT
L66        1259 S (PROTEIN-TYROSINE KINASE (L) AI)/CT
L67         386 S TYRPHOSTIN?
L68          32 S L67 AND L62
L69         241 S L67 AND L65,L66
L70          18 S L69 AND L68
L71           1 S EGFR AND L70
L72           1 S DELTAEGFR AND L70
L73       12469 S PROTEIN-TYROSINE KINASE+NT/CT
L74         460 S L73 AND L62
L75          30 S L74 AND L65
L76           1 S DELTAEGFR AND L75
L77           0 S DELTA AND L75
L78          18 S L70 AND L59,L62
L79           6 S L57 AND L78
L80           9 S L61,L63,L64,L76
L81          10 S L57 AND L66
L82          15 S L80,L81
L83           5 S APOPTOSIS/CT AND L82
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L84          7 S L61,L83
L85          8 S L82 NOT L84
L86         10 S L82 AND C4./CT
L87         13 S L84,L86
L88         12 S L87 AND L65

     FILE 'CANCERLIT' ENTERED AT 08:52:03 ON 04 FEB 1999

=> d all tot


L88  ANSWER 1 OF 12  CANCERLIT
AN   1998437957  CANCERLIT
DN   98437957
TI   STAT3 mediates the survival signal in oncogenic ras-transfected intestinal
     epithelial cells.
AU   Zushi S; Shinomura Y; Kiyohara T; Miyazaki Y; Kondo S; Sugimachi M;
     Higashimoto Y; Kanayama S; Matsuzawa Y
CS   Second Department of Internal Medicine, Osaka University Medical School,
     Suita, Japan. fwgj9902@mb.infoweb.or.jp
SO   INTERNATIONAL JOURNAL OF CANCER, (1998). Vol. 78, No. 3, pp. 326-30.
     Journal code: GQU. ISSN: 0020-7136.
DT   Journal; Article; (JOURNAL ARTICLE)
FS   MEDL; L; Priority Journals; Cancer Journals
LA   English
OS   MEDLINE 98437957
EM   199812
AB   The oncogenic ras mutation is a common and critical step in
     gastrointestinal carcinogenesis. In a previous study, we demonstrated that
     oncogenic ras activated the EGF-related peptide autocrine loop and that
     the apoptosis resistance observed in the oncogenic ras-stimulated cell
     (IEC-ras cell) was dependent on this activated EGF-related peptide
     autocrine loop. STATs (signal transducers and activators of
     transcription), first identified as intracellular signal transducers
     stimulated by cytokines, are known to also be activated by EGF. However,
     the role of STATs in the survival signal of IEC-ras cells is not clear. In
     the present study, we demonstrate that STAT3 is constitutively activated
     in ras-stimulated cells and that STAT3 activation is considerably
     suppressed by the EGF-specific receptor kinase inhibitor AG
     1478. We also show that disruption of the STAT3 pathway by
     introduction of a dominant-negative STAT3 mutant abolishes the apoptosis
     resistance against UVC and MMC treatment observed in IEC-ras cells without
     affecting proliferation. Moreover, the expression of Bcl-2 and Bcl-xL,
     apoptosis-suppressive proteins, is reduced in dominant-negative
     STAT3-transfected cells. Thus, STAT3 appears to be an important mediator
     of the antiapoptotic signal in IEC-ras cells.
CT   Check Tags: Animal
      Acute-Phase Proteins: ME, metabolism
      Cell Line
      Cell Survival
     *Cell Transformation, Neoplastic
      DNA Fragmentation
     *DNA-Binding Proteins: ME, metabolism
      Enzyme Inhibitors: PD, pharmacology
      Epidermal Growth Factor Receptor Protein-Tyrosine Kinase: AI,
     antagonists & inhibitors
      Epidermal Growth Factor-Urogastrone: PD, pharmacology
      Epidermal Growth Factor-Urogastrone: PH, physiology
     *Genes, ras
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*Intestinal Mucosa: CY, cytology
*Intestinal Mucosa: PH, physiology
Phosphorylation
Proto-Oncogene Proteins c-bcl-2: BI, biosynthesis
Rats
*Signal Transduction
*Trans-Activators: ME, metabolism
Transfection
Tyrphostins: PD, pharmacology

RN **170449-18-0 (tyrphostin AG 1478)**; 62229-50-9 (Epidermal Growth Factor-Urogastrone)

CN EC 2.7.1.- (Epidermal Growth Factor Receptor Protein-Tyrosine Kinase); 0 (bcl-x protein); 0 (gamma-activated factor, 91-kD); 0 (Acute-Phase Proteins); 0 (DNA-Binding Proteins); 0 (Enzyme Inhibitors); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Stat3 protein); 0 (Trans-Activators); 0 (Tyrphostins)

L88 ANSWER 2 OF 12 CANCERLIT

AN 1998245148 CANCERLIT

DN 98245148

TI Drug resistance of human glioblastoma cells conferred by a tumor-specific mutant epidermal growth factor receptor through modulation of Bcl-XL and caspase-3-like proteases.

AU **Nagane M; Levitzki A; Gazit A; Cavenee W K; Huang H J**

CS Ludwig Institute for Cancer Research, University of California at San Diego, La Jolla, CA 92093-0660, USA.

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998). Vol. 95, No. 10, pp. 5724-9.
Journal code: PV3. ISSN: 0027-8424.

DT Journal; Article; (JOURNAL ARTICLE)

FS MEDL; Cancer Journals; Cancer Journals; L; Priority Journals

LA English

OS MEDLINE 98245148

EM 199807

AB Alterations of the epidermal growth factor receptor (EGFR) gene occur frequently in human malignant gliomas. The most common of these is deletion of exons 2-7, resulting in truncation of the extracellular domain (**DeltaEGFR** or EGFRvIII), which occurs in a large fraction of de novo malignant gliomas (but not in progressive tumors or those lacking p53 function) and enhances tumorigenicity, in part by decreasing apoptosis through up-regulation of Bcl-XL. Here, we demonstrate that the **DeltaEGFR** concomitantly confers resistance to the chemotherapeutic drug cisplatin (CDDP) by suppression of CDDP-induced apoptosis. Expression of Bcl-XL was elevated in U87MG.**DeltaEGFR** cells prior to and during CDDP treatment, whereas it decreased considerably in CDDP-treated parental cells. CDDP-induced activation of caspase-3-like proteases was suppressed significantly in U87MG.**DeltaEGFR** cells. These responses were highly specific to constitutively kinase-active **DeltaEGFR**, because overexpression of kinase-deficient **DeltaEGFR** (DK) or wild-type EGFR had no such effects. Correspondingly, **DeltaEGFR** specific tyrosine kinase inhibitors reduced Bcl-XL expression and potentiated CDDP-induced apoptosis in U87MG. **DeltaEGFR** cells. Ectopic overexpression of Bcl-XL in parental U87MG cells also resulted in suppression of both caspase activation and apoptosis induced by CDDP. These results may have important clinical implications for the use of CDDP in the treatment of those malignant gliomas expressing **DeltaEGFR**.

CT Check Tags: Human; Support, Non-U.S. Gov't

Antineoplastic Agents: TU, therapeutic use
Apoptosis: DE, drug effects
Cisplatin: TU, therapeutic use
*Cysteine Proteinases: ME, metabolism
Drug Resistance, Neoplasm
Enzyme Activation
Enzyme Inhibitors: PD, pharmacology
*Enzyme Precursors: ME, metabolism
Glioblastoma: DT, drug therapy
Glioblastoma: EN, enzymology
***Glioblastoma: GE, genetics**
Nitriles: PD, pharmacology
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
*Proto-Oncogene Proteins c-bcl-2: ME, metabolism
Quinazolines: PD, pharmacology
***Receptors, Epidermal Growth Factor-Urogastrone: GE, genetics**
Tumor Cells, Cultured
RN **15663-27-1 (Cisplatin); 170449-18-0 (tyrphostin AG 1478)**
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 3.4.22 (Cysteine Proteinases); EC 3.4.22.- (CPP32 protein); 0 (bcl-x protein); 0 (Antineoplastic Agents); 0 (Enzyme Inhibitors); 0 (Enzyme Precursors); 0 (Nitriles); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Quinazolines); 0 (Receptors, Epidermal Growth Factor-Urogastrone)

L88 ANSWER 3 OF 12 CANCERLIT
AN 1998224102 CANCERLIT
DN 98224102
TI Preferential inhibition of glioblastoma cells with wild-type epidermal growth factor receptors by a novel tyrosine kinase inhibitor ethyl-2,5-dihydroxycinnamate.
AU Han Y; Caday C G; Umezawa K; Nanda A
CS Department of Neurosurgery, Louisiana State University Medical Center, Shreveport 71130, USA.
SO ONCOLOGY RESEARCH, (1997). Vol. 9, No. 11-12, pp. 581-7.
Journal code: BBN. ISSN: 0965-0407.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 98224102
EM 199807
AB Epidermal growth factor receptor (EGFR) gene overexpression and mutations play an important role in the pathogenesis of a variety of malignant human cancers. In this study, we tested the effects of a novel EGFR tyrosine kinase inhibitor, ethyl-2,5-dihydroxycinnamate (EtDHC), against related human glioblastoma cell lines expressing specific forms of EGFR gene mutations. EtDHC more potently inhibited cell growth and DNA synthesis in glioblastoma cells with endogenous or overexpressed wild-type EGFR compared with those with truncated EGFR, by preferentially inhibiting the tyrosine kinase activity and autophosphorylation of the wild-type EGFR. Higher concentrations of EtDHC were required to inhibit cells expressing the truncated EGFR. These findings are the reverse of another highly specific tyrosine kinase inhibitor, tyrphostin **AG 1478**, which preferentially inhibited glioblastoma cells with truncated EGFR compared with those with wild-type EGFR. The differential susceptibility of various glioblastoma cells to highly specific tyrosine kinase inhibitors is significant because human gliomas are composed of heterogeneous cells with subsets of cells expressing specific gene mutations. This cellular heterogeneity could be one of the reasons why tumor cells are resistant to chemotherapy. Thus, EtDHC, especially when in

combination with drugs targeting other specific gene mutations (such as tyrphostin **AG 1478**), holds a significant potential for chemotherapy for human glioblastomas.

CT Check Tags: Human; Support, Non-U.S. Gov't
Cell Division: DE, drug effects
*Cinnamates: PD, pharmacology
DNA Replication: DE, drug effects
DNA, Neoplasm: BI, biosynthesis
*Enzyme Inhibitors: PD, pharmacology
***Glioblastoma: PA, pathology**
Molecular Weight
Phosphorylation
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
***Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism**
Tumor Cells, Cultured

RN 40931-15-5 (ethyl 2,5-dihydroxycinnamate)

CN EC 2.7.1.112 (Protein-Tyrosine Kinase); 0 (Cinnamates); 0 (DNA, Neoplasm); 0 (Enzyme Inhibitors); 0 (Receptors, Epidermal Growth Factor-Urogastrone)

L88 ANSWER 4 OF 12 CANCERLIT

AN 1998112829 CANCERLIT

DN 98112829

TI Constitutive activation of c-Jun N-terminal kinase by a mutant epidermal growth factor receptor.

AU Antonyak M A; Moscatello D K; Wong A J

CS Microbiology and Immunology, Kimmel Cancer Institute, Thomas Jefferson University, Philadelphia, Pennsylvania 19107, USA.

NC CA51093 (NCI)
CA69495 (NCI)
5-T32-DK07705-04 (NIDDK)

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998). Vol. 273, No. 5, pp. 2817-22.
Journal code: HIV. ISSN: 0021-9258.

DT Journal; Article; (JOURNAL ARTICLE)

FS MEDL; Cancer Journals; L; Priority Journals

LA English

OS MEDLINE 98112829

EM 199803

AB Epidermal growth factor receptor (EGF) variant type III (EGFRvIII) is a constitutively active, naturally occurring mutation of the EGF receptor that is found in many types of human tumors. When overexpressed in NIH3T3 fibroblasts, EGFRvIII induces transformation by enhancing cell growth and reducing apoptosis. Analysis of downstream signaling pathways has revealed that extracellular signal-regulated kinase activity is down-regulated, raising doubt as to the significance of this pathway in promoting transformation. We investigated whether the c-Jun N-terminal kinase (JNK) pathway was affected by EGFRvIII. NIH3T3 cells expressing EGFRvIII exhibited a high basal level of JNK activity, which was not present in cells overexpressing the normal EGF receptor. Treatment of cells overexpressing EGFRvIII with inhibitors of the EGF receptor or phosphatidylinositol 3-kinase resulted in the down-regulation of JNK activity. Furthermore, the down-regulation of JNK activity was associated with a loss of properties related to transformation, and there was no evidence for JNK activity in the promotion of apoptosis in these cells. These findings implicate constitutive activation of the JNK pathway in transformation by EGFRvIII.

CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Apoptosis
*Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism

***Cell Transformation, Neoplastic: GE, genetics**
Down-Regulation (Physiology)
Enzyme Activation
Mice
Mutation
Nitriles: PD, pharmacology
Protein-Tyrosine-Phosphatase: AI, antagonists & inhibitors
Quinazolines: PD, pharmacology
Receptors, Epidermal Growth Factor-Urogastrone: AI, antagonists & inhibitors
***Receptors, Epidermal Growth Factor-Urogastrone: GE, genetics**
Signal Transduction
Transfection
1-Phosphatidylinositol 3-Kinase: AI, antagonists & inhibitors
3T3 Cells
RN **170449-18-0 (tyrphostin AG 1478)**
CN EC 2.7.1.137 (1-Phosphatidylinositol 3-Kinase); EC 2.7.10.- (c-Jun amino-terminal kinase); EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 3.1.3.48 (Protein-Tyrosine-Phosphatase); 0 (Nitriles); 0 (Quinazolines); 0 (Receptors, Epidermal Growth Factor-Urogastrone)

L88 ANSWER 5 OF 12 CANCERLIT
AN 1998078372 CANCERLIT
DN 98078372
TI Inhibition of transforming growth factor alpha stimulation of human squamous cell carcinoma of the head and neck with anti-TGF-alpha antibodies and tyrphostin.
AU Solorzano C C; Jones S C; Pettitjean M; O'Daniel T G; Auffenberg T; Woost P G; Copeland E M 3rd; Moldawer L L; Schultz G S; MacKay S L
CS Department of Biochemistry, University of Louisville, Kentucky, USA.
NC EY05587 (NEI)
GM 40586 (NIGMS)
GM 52532 (NIGMS)
SO ANNALS OF SURGICAL ONCOLOGY, (1997). Vol. 4, No. 8, pp. 670-84.
Journal code: B9R. ISSN: 1068-9265.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 98078372
EM 199803
AB BACKGROUND: Transforming growth factor alpha (TGF-alpha) and its receptor (EGF-R) may regulate normal and malignant epithelial cell growth by an autocrine mechanism. We investigated the role of TGF-alpha in regulating head and neck SCC tumor growth. METHODS: TGF-alpha and EGF-R levels were measured in 7 SCC cell lines and 14 SCC biopsies by RIA, Scatchard, and Western analysis. TGF-alpha autocrine stimulation of DNA synthesis in SCC cell lines was assessed by incubation with TGF-alpha neutralizing antibodies and tyrphostin **AG 1478**, a selective and potent inhibitor of EGF-R kinase. RESULTS: All SCC cell lines synthesized TGF-alpha and expressed elevated EGF-R levels compared to normal keratinocytes. Twelve of the 14 SCC biopsies contained TGF-alpha protein and 8 had specific EGF-R. Exogenous TGF-alpha or EGF significantly increased DNA synthesis in 4 of 5 SCC cell lines. TGF-alpha neutralizing antibodies or tyrphostin **AG 1478** reduced DNA synthesis in the two SCC cell lines (FaDu and SCC9) tested. CONCLUSIONS: These results indicate that SCC cell lines and tumors usually synthesize TGF-alpha, have elevated levels of EGF-R, and are mitogenically stimulated by a TGF-alpha autocrine system. Selective inhibition of the TGF-alpha system by EGF-R kinase inhibitors or TGF-alpha neutralizing antibodies may

be useful strategies for treating SCC that overexpress TGF-alpha and its receptor.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Autocrine Communication: PH, physiology
***Carcinoma, Squamous Cell: PP, physiopathology**
DNA, Neoplasm: BI, biosynthesis
***Head and Neck Neoplasms: PP, physiopathology**
***Protein-Tyrosine Kinase: AI, antagonists & inhibitors**
***Receptors, Epidermal Growth Factor-Urogastrone: PH, physiology**
Regression Analysis
*Transforming Growth Factor alpha: AI, antagonists & inhibitors
Tumor Cells, Cultured

CN EC 2.7.1.112 (Protein-Tyrosine Kinase); 0 (DNA, Neoplasm); 0 (Receptors, Epidermal Growth Factor-Urogastrone); 0 (Transforming Growth Factor alpha)

L88 ANSWER 6 OF 12 CANCERLIT
AN 1998060597 CANCERLIT
DN 98060597
TI Role of heparin-binding EGF-related peptides in proliferation and apoptosis of activated ras-stimulated intestinal epithelial cells.
AU Zushi S; Shinomura Y; Kiyohara T; Miyazaki Y; Tsutsui S; Sugimachi M; Higashimoto Y; Kanayama S; Matsuzawa Y
CS Second Department of Internal Medicine, Osaka University Medical School, Suita, Japan.
SO INTERNATIONAL JOURNAL OF CANCER, (1997). Vol. 73, No. 6, pp. 917-23. Journal code: GQU. ISSN: 0020-7136.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; Cancer Journals; L; Priority Journals
LA English
OS MEDLINE 98060597
EM 199802
AB The ras mutation is a common and critical step in carcinogenesis. Autocrine growth factors are also known to play an important role in cancer cell growth and transformation. However, the contribution of autocrine growth factors in regulation of proliferation and apoptosis of activated ras-stimulated intestinal epithelium is not fully understood. Therefore, we constructed activated ras-transfected intestinal epithelial cell clones (IEC-ras) to examine the role of epidermal growth factor (EGF)-related peptides in the behavior of IEC-ras. Overexpression of EGF family growth factors (transforming growth factor alpha, heparin-binding EGF-like growth factor, amphiregulin and betacellulin) and stronger phosphorylation of the EGF receptor was observed in IEC-ras compared with control cells. IEC-ras proliferated more rapidly than control cells, and a specific EGF receptor kinase inhibitor, **AG 1478**, abolished the increased proliferation of IEC-ras. Heparitinase and chlorate also prevented increased proliferation of IEC-ras. Additionally, IEC-ras expressed more bcl-2 and was more resistant to apoptosis induction by UV radiation and mitomycin C. **AG 1478** suppressed bcl-2 expression and inhibited resistance to apoptosis of IEC-ras. Heparitinase and chlorate had effects similar to those of **AG 1478**. Our data indicate that heparin-binding EGF family growth factors play an important role in both increased proliferation and resistance to apoptosis of ras-stimulated intestinal epithelial cells.
CT Check Tags: Animal; Human
***Apoptosis**
Apoptosis: GE, genetics
Autocrine Communication
Cell Division: GE, genetics
Cells, Cultured

Chlorates: PD, pharmacology
Culture Media, Conditioned
Epidermal Growth Factor-Urogastrone: ME, metabolism
Genes, ras: GE, genetics
Glycoproteins: ME, metabolism
Growth Substances: ME, metabolism
*Intestinal Mucosa: CY, cytology
*Intestinal Mucosa: ME, metabolism
Nitriles: PD, pharmacology
Phosphorylation
Polysaccharide-Lyases: PD, pharmacology
Protein-Tyrosine-Phosphatase: AI, antagonists & inhibitors
Proto-Oncogene Proteins c-bcl-2: ME, metabolism
Quinazolines: PD, pharmacology
RNA: AN, analysis
Rats
Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism
Transfection
Transforming Growth Factor alpha: ME, metabolism
Tumor Cells, Cultured
Up-Regulation (Physiology)
ras Proteins: ME, metabolism

RN 117147-70-3 (amphiregulin); 149176-25-0 (heparin-binding EGF-like growth factor); 62229-50-9 (Epidermal Growth Factor-Urogastrone); 63231-63-0 (RNA)

CN EC 3.1.3.48 (Protein-Tyrosine-Phosphatase); EC 4.2.2. (Polysaccharide-Lyases); EC 4.2.2.8 (heparitinsulfate lyase); 0 (betacellulin); 0 (ras Proteins); **0 (tyrphostin AG 1478)**; 0 (Chlorates); 0 (Culture Media, Conditioned); 0 (Glycoproteins); 0 (Growth Substances); 0 (Nitriles); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Quinazolines); 0 (Receptors, Epidermal Growth Factor-Urogastrone); 0 (Transforming Growth Factor alpha)

L88 ANSWER 7 OF 12 CANCERLIT

AN 97433113 CANCERLIT

DN 97433113

TI Inhibitors of epidermal growth factor receptor kinase and of cyclin-dependent kinase 2 activation induce growth arrest, differentiation, and apoptosis of human papilloma virus 16-immortalized human keratinocytes.

AU Ben-Bassat H; Rosenbaum-Mitrani S; Hartzstark Z; Shlomai Z; Kleinberger-Doron N; **Gazit A**; Plowman G; Levitzki R; Tsvieli R; **Levitzki A**

CS Laboratory of Experimental Surgery, Hadassah University Hospital, Jerusalem, Israel.

SO CANCER RESEARCH, (1997). Vol. 57, No. 17, pp. 3741-50. Journal code: CNF. ISSN: 0008-5472.

DT Journal; Article; (JOURNAL ARTICLE)

FS MEDL; Cancer Journals; L; Priority Journals

LA English

OS MEDLINE 97433113

EM 199710

AB Human papilloma virus 16 (HPV 16) is associated with cervical cancer and is therefore considered a major health risk for women. Immortalization of keratinocytes induced by HPV infection is largely due to the binding of p53 and Rb by the the viral oncoproteins E6 and E7, respectively, and is driven to a large extent by a transforming growth factor alpha/amphiregulin epidermal growth factor receptor autocrine loop. In this study, we show that the growth of HPV 16-immortalized human

keratinocytes can be blocked by a selective epidermal growth factor receptor kinase inhibitor, **AG 1478**, and by AG 555, a blocker of cyclin-dependent kinase 2 (Cdk2) activation. **AG 1478** induces a massive increase in the Cdk2 protein inhibitors p27 and p21, whereas AG 555 appears to have a different mechanism of action, inhibiting the activation of Cdk2. Growth arrest induced by **AG 1478** and AG 555 is accompanied by up to 20% of cells undergoing apoptosis. Following **AG 1478** treatment but not AG 555 treatment, up to 50% of cells undergo terminal keratinocyte differentiation as determined by filaggrin expression and by the decline in the expression of cytokeratin 14. The growth-arresting properties of **AG 1478** and AG 555 identifies them as possible lead antipapilloma agents.

CT Check Tags: Human; Support, Non-U.S. Gov't
Antibodies: PD, pharmacology
Apoptosis: DE, drug effects
*Benzylidene Compounds: PD, pharmacology
Cell Cycle: DE, drug effects
Cell Differentiation: DE, drug effects
Cell Division: DE, drug effects
Cell Line, Transformed
*Cyclin-Dependent Kinases: AI, antagonists & inhibitors
*Enzyme Inhibitors: PD, pharmacology
***Epidermal Growth Factor Receptor Protein-Tyrosine Kinase: AI, antagonists & inhibitors**
Keratinocytes: CY, cytology
*Keratinocytes: DE, drug effects
Keratinocytes: VI, virology
*Nitriles: PD, pharmacology
*Papillomavirus, Human
Phosphorylation: DE, drug effects
*Quinazolines: PD, pharmacology
Receptors, Epidermal Growth Factor-Urogastrone: IM, immunology
Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism

CN EC 2.7.1.- (Epidermal Growth Factor Receptor Protein-Tyrosine Kinase); **0 (tyrphostin AG 1478)**; 0 (tyrphostin AG 555); 0 (Antibodies); 0 (Benzylidene Compounds); 0 (Cyclin-Dependent Kinases); 0 (Enzyme Inhibitors); 0 (Nitriles); 0 (Quinazolines); 0 (Receptors, Epidermal Growth Factor-Urogastrone)

L88 ANSWER 8 OF 12 CANCERLIT
AN 97413610 CANCERLIT
DN 97413610
TI Two- and three-dimensional cell structures govern epidermal growth factor survival function in human bladder carcinoma cell lines.
AU Dangles V; Femenia F; Laine V; Berthelemy M; Le Rhun D; Poupon M F; Levy D; Schwartz-Cornil I
CS URA INRA-DGER d'Immunopathologie Cellulaire et Moleculaire, Ecole Nationale Veterinaire, Maisons Alfort, France.
SO CANCER RESEARCH, (1997). Vol. 57, No. 16, pp. 3360-4.
Journal code: CNF. ISSN: 0008-5472.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; Cancer Journals; L; Priority Journals
LA English
OS MEDLINE 97413610
EM 199710
AB Human bladder carcinomas often express high levels of the epidermal growth factor (EGF) receptor. In three human bladder carcinoma cell lines (OBR, T24, and 647V), we show that two EGF receptor ligands, namely EGF and

transforming growth factor alpha, enhanced the apoptosis due to serum starvation on cells cultured as monolayers. Conversely, EGF and transforming growth factor alpha prevented apoptosis when the same serum-starved cells were cultured as three-dimensional spheroids. Both stimulation and inhibition of apoptosis by EGF were associated with p21 WAF1/CIP1 overexpression. In 647V spheroids, EGF protection against radiation-induced apoptosis was negated by genistein and tyrphostin **AG1478**, suggesting that blockade of the EGF signal transduction in patients with bladder cancer may improve the radiotherapy efficacy.

CT Check Tags: Human; Support, Non-U.S. Gov't
***Apoptosis: DE, drug effects**
Apoptosis: RE, radiation effects
***Bladder Neoplasms: ME, metabolism**
***Bladder Neoplasms: PA, pathology**
Culture Media, Serum-Free
Cyclins: ME, metabolism
*Epidermal Growth Factor-Urogastrone: PD, pharmacology
Isoflavones: PD, pharmacology
*Neoplasm Proteins: ME, metabolism
Nitriles: PD, pharmacology
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
Quinazolines: PD, pharmacology
***Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism**
*Spheroids: ME, metabolism
*Spheroids: PA, pathology
Time Factors
*Transforming Growth Factor alpha: PD, pharmacology
Tumor Cells, Cultured
Up-Regulation (Physiology)

RN 446-72-0 (Genistein); 62229-50-9 (Epidermal Growth Factor-Urogastrone)

CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **0 (tyrphostin AG 1478)**; 0 (Cip1 protein); 0 (Culture Media, Serum-Free); 0 (Cyclins); 0 (Isoflavones); 0 (Neoplasm Proteins); 0 (Nitriles); 0 (Quinazolines); 0 (Receptors, Epidermal Growth Factor-Urogastrone); 0 (Transforming Growth Factor alpha)

L88 ANSWER 9 OF 12 CANCERLIT
AN 97214613 CANCERLIT
DN 97214613
TI Inhibition of tyrosine kinase activity decreases expression of surfactant protein A in a human lung adenocarcinoma cell line independent of epidermal growth factor receptor.
AU Klein J M; McCarthy T A
CS Department of Pediatrics, University of Iowa, Iowa City 52242-1083, USA. jonathan-klein@uiowa.edu
NC P30 HD27748 (NICHD)
R29 HL52055 (NHLBI)
SO BIOCHIMICA ET BIOPHYSICA ACTA, (1997). Vol. 1355, No. 3, pp. 218-30. Journal code: A0W. ISSN: 0006-3002.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; Cancer Journals; L; Priority Journals
LA English
OS MEDLINE 97214613
EM 199705
AB Epidermal growth factor (EGF) enhances fetal lung development in vivo and in vitro. Ligand binding to the EGF receptor stimulates an intrinsic receptor tyrosine kinase initiating a signal transduction cascade. We hypothesized that blocking EGF receptor function with tyrosine kinase inhibitors would decrease the expression of surfactant protein A in human

pulmonary epithelial cells. Human pulmonary adenocarcinoma cells (NCI-H441) were exposed to genistein (a broad range inhibitor of tyrosine kinases) and tyrphostin **AG1478** (a specific inhibitor of EGF receptor tyrosine kinase). Genistein significantly decreased surfactant protein A (SP-A) and SP-A mRNA levels in H441 cells without affecting cell viability. The inhibitory effect of genistein on SP-A content was reversible. In contrast, tyrphostin **AG1478** had no effect on SP-A levels despite a greater inhibitory effect than genistein on EGF receptor tyrosine autophosphorylation. Furthermore, treatment of H441 cells with exogenous EGF did not increase SP-A content or mRNA levels beyond baseline. We conclude that inhibition of tyrosine kinase activity other than the EGF receptor decreases the expression of surfactant protein A at a pretranslational level in human pulmonary adenocarcinoma cells. These results suggest the importance of tyrosine kinases in modulating human SP-A synthesis.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Benzylidene Compounds: PD, pharmacology
Binding, Competitive
Blotting, Northern
Blotting, Western
Cell Survival: DE, drug effects
Enzyme Inhibitors: PD, pharmacology
***Epidermal Growth Factor Receptor Protein-Tyrosine Kinase: AI, antagonists & inhibitors**
Epidermal Growth Factor Receptor Protein-Tyrosine Kinase: ME, metabolism
*Epidermal Growth Factor-Urogastrone: ME, metabolism
Epidermal Growth Factor-Urogastrone: PD, pharmacology
Isoflavones: PD, pharmacology
Lung: EN, enzymology
*Lung: ME, metabolism
Lung Neoplasms
Nitriles: PD, pharmacology
Phosphorylation
***Protein-Tyrosine Kinase: AI, antagonists & inhibitors**
Proteolipids: GE, genetics
*Proteolipids: ME, metabolism
Pulmonary Surfactants: GE, genetics
*Pulmonary Surfactants: ME, metabolism
RNA, Messenger: ME, metabolism
***Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism**
Tumor Cells, Cultured

RN 446-72-0 (Genistein); 62229-50-9 (Epidermal Growth Factor-Urogastrone)

CN EC 2.7.1.- (Epidermal Growth Factor Receptor Protein-Tyrosine Kinase); EC 2.7.1.112 (Protein-Tyrosine Kinase); 0 (pulmonary surfactant-associated protein); **0 (tyrphostin AG 1478)**; 0 (Benzylidene Compounds); 0 (Enzyme Inhibitors); 0 (Isoflavones); 0 (Nitriles); 0 (Proteolipids); 0 (Pulmonary Surfactants); 0 (Receptors, Epidermal Growth Factor-Urogastrone); 0 (RNA, Messenger)

L88 ANSWER 10 OF 12 CANCERLIT

AN 96354597 CANCERLIT

DN 96354597

TI Tyrphostin **AG 1478** preferentially inhibits human glioma cells expressing truncated rather than wild-type epidermal growth factor receptors.

AU Han Y; Caday C G; Nanda A; **Cavenee W K; Huang H J**

CS Department of Neurosurgery, Louisiana State University Medical Center, Shreveport 71130, USA.

SO CANCER RESEARCH, (1996). Vol. 56, No. 17, pp. 3859-61.
Journal code: CNF. ISSN: 0008-5472.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; Cancer Journals; L; Priority Journals
LA English
OS MEDLINE 96354597
EM 199611
AB The effects of a new epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, tyrphostin **AG 1478**, were tested on three related human glioma cell lines: U87MG, which expressed endogenous wild-type (wt) EGFR, and two retrovirally infected U87MG cell populations which over-expressed either wt (U87MG.wtEGFR) or truncated EGFR (U87MG. delta EGFR). Although **AG 1478** inhibited cell growth, DNA synthesis, EGFR tyrosine kinase activity, and receptor autophosphorylation of each cell line in a dose-dependent manner, it was significantly more potent in U87MG. delta EGFR cells than in the other two cell lines. The increased inhibitory response of U87MG. delta EGFR cells was due to a greater sensitivity of the constitutively autophosphorylated Mr 140,000 and 155,000 delta EGFR species to **AG 1478**. These results suggest that **AG 1478** is a relatively specific inhibitor of the delta EGFR, and this finding may have important therapeutic implications since the delta EGFR occurs frequently in glioblastomas and in breast, lung, and ovarian cancers.
CT Check Tags: Comparative Study; Human
*Benzylidene Compounds: PD, pharmacology
Cell Division: DE, drug effects
*Enzyme Inhibitors: PD, pharmacology
Gene Amplification
***Glioma: DT, drug therapy**
***Glioma: UL, ultrastructure**
Mutation
*Nitriles: PD, pharmacology
Phosphorylation
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
***Receptors, Epidermal Growth Factor-Urogastrone: AI, antagonists & inhibitors**
Receptors, Epidermal Growth Factor-Urogastrone: GE, genetics
Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism
Tumor Cells, Cultured
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **0 (tyrphostin AG 1478)**; 0 (Benzylidene Compounds); 0 (Enzyme Inhibitors); 0 (Nitriles); 0 (Receptors, Epidermal Growth Factor-Urogastrone)

L88 ANSWER 11 OF 12 CANCERLIT
AN 96021291 CANCERLIT
DN 96021291
TI Prolonged induction of p21Cip1/WAF1/CDK2/PCNA complex by epidermal growth factor receptor activation mediates ligand-induced A431 cell growth inhibition.
AU Fan Z; Lu Y; Wu X; DeBlasio A; Koff A; Mendelsohn J
CS Program of Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York 10021, USA.
NC CA42060 (NCI)
CA37641 (NCI)
SO JOURNAL OF CELL BIOLOGY, (1995). Vol. 131, No. 1, pp. 235-42.
Journal code: HMV. ISSN: 0021-9525.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; Cancer Journals; L; Priority Journals
LA English

OS MEDLINE 96021291
EM 199512
AB Proliferation of some cultured human tumor cell lines bearing high numbers of epidermal growth factor (EGF) receptors is paradoxically inhibited by EGF in nanomolar concentrations. In the present study, we have investigated the biochemical mechanism of growth inhibition in A431 human squamous carcinoma cells exposed to exogenous EGF. In parallel, we studied a selected subpopulation, A431-F, which is resistant to EGF-mediated growth inhibition. We observed a marked reduction in cyclin-dependent kinase-2 (CDK2) activity when A431 and A431-F cells were cultured with 20 nM EGF for 4 h. After further continuous exposure of A431 cells to EGF, the CDK2 activity remained at a low level and was accompanied by persistent G1 arrest. In contrast, the early reduced CDK2 activity and G1 accumulation in A431-F cells was only transient. We found that, at early time points (4-8 h), EGF induces p21Cip1/WAF1 mRNA and protein expression in both EGF-sensitive A431 cells and EGF-resistant A431-F cells. But only in A431 cells, was p21Cip1/WAF1 expression sustained at a significantly increased level for up to 5 d after addition of EGF. Induction of p21Cip1/WAF1 by EGF could be inhibited by a specific EGF receptor tyrosine kinase inhibitor, tyrphostin **AG1478**, suggesting that p21Cip1/WAF1 induction was a consequence of receptor tyrosine kinase activation by EGF. We also demonstrated that the increased p21Cip1/WAF1 was associated with both CDK2 and proliferating cell nuclear antigen (PCNA). Taken together, our results demonstrate that p21Cip1/WAF1 is an important mediator of EGF-induced G1 arrest and growth inhibition in A431 cells.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Carcinoma, Squamous Cell
Cell Cycle: DE, drug effects
Cyclin-Dependent Kinases: AI, antagonists & inhibitors
*Cyclin-Dependent Kinases: ME, metabolism
*Cyclins: ME, metabolism
*Enzyme Inhibitors: ME, metabolism
Epidermal Growth Factor-Urogastrone: PD, pharmacology
Growth Inhibitors: PH, physiology
Nitriles: PD, pharmacology
Phenols: PD, pharmacology
*Proliferating Cell Nuclear Antigen: ME, metabolism
Protein-Serine-Threonine Kinases: AI, antagonists & inhibitors
*Protein-Serine-Threonine Kinases: ME, metabolism
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
***Receptors, Epidermal Growth Factor-Urogastrone: PH, physiology**
Signal Transduction: PH, physiology
Tumor Cells, Cultured: EN, enzymology
RN 3735-59-9 (tyrphostin 47); 62229-50-9 (Epidermal Growth Factor-Urogastrone)
CN EC 2.7.1.- (CDK2 protein); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.10 (Protein-Serine-Threonine Kinases); 0 (Cip1 protein); 0 (Cyclin-Dependent Kinases); 0 (Cyclins); 0 (Enzyme Inhibitors); 0 (Growth Inhibitors); 0 (Nitriles); 0 (Phenols); 0 (Proliferating Cell Nuclear Antigen); 0 (Receptors, Epidermal Growth Factor-Urogastrone)

L88 ANSWER 12 OF 12 CANCERLIT
AN 95045533 CANCERLIT
DN 95045533
TI Epidermal-growth-factor-dependent activation of the src-family kinases.
AU Osherov N; **Levitzki A**
CS Department of Biological Chemistry, Alexander Silberman Institute of Life Science, Hebrew University of Jerusalem, Israel.

SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1994). Vol. 225, No. 3, pp. 1047-53.
Journal code: EMZ. ISSN: 0014-2956.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; Cancer Journals; L; Priority Journals
LA English
OS MEDLINE 95045533
EM 199501
AB The precise role of src-type kinases as signal transducers has been under intensive investigation but only in a few instances has their role been revealed in any detail. Thus, src, fyn and yes are activated upon stimulation by platelet-derived growth factor or colony-stimulating factor in cells expressing high levels of these receptors. Activation of src-family kinases by other receptor tyrosine kinases such as the epidermal-growth-factor (EGF) receptor has not been directly demonstrated. In this report, we demonstrate EGF-dependent activation of src-family tyrosine kinases in NIH3T3 cells overexpressing the human EGF receptor. Activation is rapid (< 1 min) and persistent (up to 16 h). Furthermore, we show a correlation between the level of EGF receptor expressed and the degree of src-family kinase activation. We show that src-family kinase activity is also activated by addition of EGF to PC12 cells, which endogenously express relatively high levels of EGF receptor. Most strikingly, we show that A431 cells, which endogenously express very high levels of EGF receptor, show 10-fold elevated src-family kinase activity as compared to DHER14 cells, and that this activity is constitutive. This activity is completely blocked by **AG1478**, a specific inhibitor of the EGF-receptor tyrosine kinase activity, pointing to a direct link between overexpression of the EGF receptor and enhanced src-family kinase activity. Our findings suggest that EGF-dependent src-family kinase activity is detectable only when the levels of EGF receptor reach a specific level. Additionally, high levels of EGF receptor, as in A431 cells, may contribute to the elevated activation of src-family kinases. Sustained src-family kinase activation, similar to that seen in v-src-transformed cells, may play a role in tumorogenesis and tumor maintenance.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Enzyme Activation: DE, drug effects
*Epidermal Growth Factor-Urogastrone: PD, pharmacology
Mice
PC12 Cells
*Protein-Tyrosine Kinase: ME, metabolism
*Proto-Oncogene Protein pp60(c-src): ME, metabolism
Rats
Receptors, Epidermal Growth Factor-Urogastrone: GE, genetics
Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism
Signal Transduction
Transfection
3T3 Cells
RN 62229-50-9 (Epidermal Growth Factor-Urogastrone)
CN EC 2.7.1.- (Proto-Oncogene Protein pp60(c-src)); EC 2.7.1.112 (Protein-Tyrosine Kinase); 0 (Receptors, Epidermal Growth Factor-Urogastrone)

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(FILE 'CANCERLIT' ENTERED AT 08:23:18 ON 04 FEB 1999)

FILE 'CANCERLIT' ENTERED AT 08:52:03 ON 04 FEB 1999
L89 88 S L62 AND L65

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L90           7 S L66 AND L89
L91        6650 S EPIDERMAL GROWTH FACTOR-UROGASTRONE/CT
L92           7 S L89 AND L66
L93           7 S L92 AND L62
L94           5 S L90,L92,L93 NOT L88

=> d all tot
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L94 ANSWER 1 OF 5 CANCERLIT
AN 1998330492 CANCERLIT
DN 98330492
TI EGFR blockade by tyrosine kinase inhibitor or monoclonal antibody inhibits growth, directs terminal differentiation and induces apoptosis in the human squamous cell carcinoma HN5.
AU Modjtahedi H; Affleck K; Stubberfield C; Dean C
CS The Institute of Cancer Research, McElwain Laboratories, Belmont, Sutton, Surrey, UK.
SO CX5, (1998). Vol. 13, No. 2, pp. 335-42.
Journal code: CX5. ISSN: 1019-6439.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 98330492
EM 199809
AB Human squamous cell carcinomas frequently overexpress the epidermal growth factor receptor (EGFR) and this is often associated with poor prognosis in patients with these cancers. The high level of expression of the EGFR provides an important target for therapy and we and others have shown that monoclonal antibodies (mAbs) which block the activation of the receptor by the EGF family of ligands inhibit the growth of EGFR overexpressing tumours in vitro and induce the regression of established tumours grown as xenografts in athymic mice. Inhibitors of the tyrosine kinase associated with the EGFR have also been shown to block receptor activation and prevent tumour cell proliferation. Using the EGFR-overexpressing head and neck carcinoma cell line HN5, we have compared the biological consequences of treatment with an inhibitor of EGFR tyrosine kinase (PD153035) with anti-EGFR monoclonal antibodies (mAbs) ICR63 or ICR80. We found that both the anti-EGFR mAbs and the TK inhibitor produce similar biological changes namely, they inhibit the EGF and TGFa-induced tyrosine phosphorylation of the receptor and the growth in culture of HN5 cells. At concentrations above 100 nM, the TK inhibitor prevented the growth in culture of HN5 cells completely with an IC50 of 40 nM. With the anti-EGFR mAbs, growth of HN5 cells was inhibited completely at concentrations above 4 nM with an IC50 of 1 nM. More importantly we found that, like the anti-EGFR mAbs, treatment with the TK inhibitor directs HN5 cells to undergo terminal differentiation as monitored by the expression of cytokeratin 10. In addition, our results indicate that the growth inhibitory effects of the anti-EGFR agents also lead to induction of apoptosis as determined by 7-amino actinomycin D staining (7-AAD). We conclude that EGFR blockade by anti-EGFR mAbs or TK inhibitor influences the growth in culture of EGFR overexpressing tumours by directing terminal differentiation and inducing apoptosis.
CT Check Tags: Human
*Antibodies, Monoclonal: PD, pharmacology
Apoptosis: DE, drug effects
Apoptosis: PH, physiology
*Carcinoma, Squamous Cell: DT, drug therapy
Carcinoma, Squamous Cell: ME, metabolism

*Carcinoma, Squamous Cell: PA, pathology
Cell Differentiation: DE, drug effects
Cell Differentiation: PH, physiology
Cell Division: DE, drug effects
Cell Division: PH, physiology
*Enzyme Inhibitors: PD, pharmacology
*Head and Neck Neoplasms: DT, drug therapy
Head and Neck Neoplasms: ME, metabolism
*Head and Neck Neoplasms: PA, pathology
Phosphorylation
***Protein-Tyrosine Kinase: AI, antagonists & inhibitors**
*Quinazolines: PD, pharmacology
***Receptors, Epidermal Growth Factor-Urogastrone: AI, antagonists & inhibitors**
Receptors, Epidermal Growth Factor-Urogastrone: IM, immunology
Tumor Cells, Cultured
Tyrosine: ME, metabolism
RN 55520-40-6 (Tyrosine)
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); 0 (Antibodies, Monoclonal); 0 (Enzyme Inhibitors); 0 (PD 153035); 0 (Quinazolines); 0 (Receptors, Epidermal Growth Factor-Urogastrone)

L94 ANSWER 2 OF 5 CANCERLIT
AN 1998225123 CANCERLIT
DN 98225123
TI Inhibition of epidermal growth factor receptor kinase induces protease-dependent apoptosis in human colon cancer cells.
AU Karnes W E Jr; Weller S G; Adjei P N; Kottke T J; Glenn K S; Gores G J; Kaufmann S H
CS Division of Gastroenterology, Mayo Clinic, Rochester, Minnesota 55905, USA. karnes@ralph.mayo.edu
NC R29 CA71974 (NCI)
K11 CA01674 (NCI)
R01 CA69008 (NCI)
+
SO GASTROENTEROLOGY, (1998). Vol. 114, No. 5, pp. 930-9.
Journal code: FH3. ISSN: 0016-5085.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; Cancer Journals; L; Priority Journals
LA English
OS MEDLINE 98225123
EM 199806
AB BACKGROUND & AIMS: The epidermal growth factor receptor (EGFR) is under investigation as a therapeutic target for cancers. Colon cancer cell lines are variably dependent on autocrine stimulation of EGFR. We therefore examined the effects of a selective EGFR tyrosine kinase inhibitor, PD 153035, on proliferation and survival of five colon cancer cell lines whose autonomous proliferation is either EGFR ligand dependent or EGFR ligand independent. METHODS: Effects of inhibitors were screened by MTS growth assays, [3H]thymidine incorporation, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling assay, fluorescence microscopy, immunoblotting, and in vitro protease assays. RESULTS: PD 153035 caused dose-dependent cytostasis (200 nmol/L to 1 micromol/L) and apoptosis (>10 micromol/L) in ligand-dependent cell lines and caused variable apoptosis (>10 micromol/L) but no cytostasis in ligand-independent cell lines. Apoptosis induced by 10 micromol/L PD 153035 was not associated with induction of p53 protein expression but was accompanied by activation of caspases that cleave poly(ADP-ribose) polymerase, lamin B1, and Bcl-2. Inhibition of caspase 3-like protease

activity by DEVD-fluoromethylketone significantly delayed the onset of PD 153035-induced apoptosis. CONCLUSIONS: The EGFR tyrosine kinase inhibitor PD 153035 induces cytostasis and caspase-dependent apoptosis in EGFR ligand-dependent colon cancer cell lines. These observations encourage further investigation of EGFR tyrosine kinase inhibitors for treatment of colorectal neoplasms.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Apoptosis: DE, drug effects
***Apoptosis: PH, physiology**
Colonic Neoplasms: PA, pathology
*Colonic Neoplasms: PP, physiopathology
Enzyme Inhibitors: PD, pharmacology
Ligands
*Peptide Peptidohydrolases: PH, physiology
Protease Inhibitors: PD, pharmacology
Protein p53: ME, metabolism
***Protein-Tyrosine Kinase: AI, antagonists & inhibitors**
Proto-Oncogene Proteins c-bcl-2: ME, metabolism
Quinazolines: PD, pharmacology
***Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism**
Tumor Cells, Cultured: DE, drug effects

CN EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 3.4.- (Peptide Peptidohydrolases); 0 (Enzyme Inhibitors); 0 (Ligands); 0 (Protease Inhibitors); 0 (Protein p53); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (PD 153035); 0 (Quinazolines); 0 (Receptors, Epidermal Growth Factor-Urogastrone)

L94 ANSWER 3 OF 5 CANCERLIT
AN 96419427 CANCERLIT
DN 96419427
TI Epidermal growth factor-induced apoptosis in A431 cells can be reversed by reducing the tyrosine kinase activity.
AU Gulli L F; Palmer K C; Chen Y Q; Reddy K B
CS Department of Pathology, Wayne State University, Detroit, Michigan 48201, USA.
SO CELL GROWTH AND DIFFERENTIATION, (1996). Vol. 7, No. 2, pp. 173-8. Journal code: AYH. ISSN: 1044-9523.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 96419427
EM 199704
AB A431 cells overexpress epidermal growth factor receptors (EGF-Rs) and are inhibited by EGF. We show that treatment of A431 cells with 10 nM EGF induced a 15-fold increase in EGF-R autophosphorylation, leading to inhibition of cell proliferation and morphological features of apoptosis. However, at a lower concentration of EGF (0.01 nM), there is a 2-fold increase in EGF-R autophosphorylation and increased cell proliferation when compared to untreated cells. EGF treatment is associated with increased expression of c-myc and decreased expression of mutant p53 and p21/WAF protein. When A431 cells were simultaneously treated with 10 nM EGF and EGF-R antibody, there was a significant reduction in EGF-R autophosphorylation that was associated with increased cell proliferation. Based on these results, we postulate that overexpression of EGF-R could allow for selective growth advantage for tumor cells in the presence of normal or decreased ligand availability. However, excessive ligand binding would result in deregulated growth signaling, leading to growth inhibition and programmed cell death.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Antibody Specificity
***Apoptosis: DE, drug effects**
Apoptosis: PH, physiology
Cell Division: DE, drug effects
Cell Division: PH, physiology
Cell Survival: DE, drug effects
Cyclins: GE, genetics
Enzyme Inhibitors: PD, pharmacology
*Epidermal Growth Factor-Urogastrone: PD, pharmacology
Gene Expression: DE, drug effects
Gene Expression: PH, physiology
Nitriles: PD, pharmacology
Phosphorylation
Protein p53: GE, genetics
***Protein-Tyrosine Kinase: AI, antagonists & inhibitors**
Protein-Tyrosine Kinase: ME, metabolism
Proto-Oncogene Proteins c-myc: GE, genetics
Pyridines: PD, pharmacology
RNA, Messenger: AN, analysis
Receptors, Epidermal Growth Factor-Urogastrone: IM, immunology
Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism
Signal Transduction: PH, physiology
Tumor Cells, Cultured: CY, cytology
Tumor Cells, Cultured: EN, enzymology
Tumor Cells, Cultured: UL, ultrastructure

RN 136831-48-6 (RG 13022); 62229-50-9 (Epidermal Growth Factor-Urogastrone)
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); 0 (Cip1 protein); 0 (Cyclins); 0 (Enzyme Inhibitors); 0 (Nitriles); 0 (Protein p53); 0 (Proto-Oncogene Proteins c-myc); 0 (Pyridines); 0 (Receptors, Epidermal Growth Factor-Urogastrone); 0 (RNA, Messenger)

L94 ANSWER 4 OF 5 CANCERLIT
AN 96165700 CANCERLIT
DN 96165700
TI Tyrphostin induces non-apoptotic programmed cell death in colon tumor cells.
AU Szende B; Keri G; Szegedi Z; Benedeczky I; Csikos A; Orfi L; Gazit A
CS 1st Institute of Pathology and Experimental Cancer Research, Hungarian Academy of Sciences, Semmelweis University of Medicine, Budapest, Hungary.
SO CELL BIOLOGY INTERNATIONAL, (1995). Vol. 19, No. 11, pp. 903-11. Journal code: BPN. ISSN: 1065-6995.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 96165700
EM 199604
AB The programmed cell death inducing effect of the EGF receptor tyrosine kinase inhibitor alpha-cyano-3,4-dihydroxycinnamthioamide (AG213) was investigated in vitro on HT-29 human colon tumor. AG213 at concentrations between 45 to 450 microM blocks the proliferation of HT-29 cells. Morphological findings suggest that the selective tyrosine kinase inhibitor AG213 induces Clarke III type (non-lysosomal vesiculate cytoplasmic) programmed cell death; unlike ATP analog non-selective tyrosine kinase inhibitors like Genistein which were found to induce apoptosis. Cycloheximide and Actinomycin-D reduced the effect of AG213 pointing to the fact that protein and RNA synthesis are also needed for this form of cell death. Acid phosphatase activity was found in the Golgi and in the newly formed intracytoplasmic vacuoles 3 hours after AG213 treatment which disappeared by 6 hours. The induction of Clarke III cell

death by tyrosine kinase inhibitors may open a new modality to selective killing of tumor cells.

CT Check Tags: Human; Support, Non-U.S. Gov't
Acid Phosphatase: ME, metabolism
***Apoptosis: DE, drug effects**
*Catechols: PD, pharmacology
Cell Count
Cell Survival: DE, drug effects
Cycloheximide: PD, pharmacology
Dactinomycin: PD, pharmacology
*Enzyme Inhibitors: PD, pharmacology
HT29 Cells: CY, cytology
*HT29 Cells: EN, enzymology
HT29 Cells: UL, ultrastructure
*Nitriles: PD, pharmacology
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism

RN 118409-60-2 (RG 50864); 50-76-0 (Dactinomycin); 66-81-9 (Cycloheximide)

CN EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 3.1.3.2 (Acid Phosphatase); 0 (Catechols); 0 (Enzyme Inhibitors); 0 (Nitriles); 0 (Receptors, Epidermal Growth Factor-Urogastrone)

L94 ANSWER 5 OF 5 CANCERLIT

AN 95611758 CANCERLIT

DN 95611758

TI Evaluation of the biochemical targets of genistein in tumor cells (Meeting abstract).

AU Peterson T G

CS Department of Biochemistry, University of Alabama, Birmingham, AL 35294.

SO Non-serial, (1994). First International Symposium on the Role of Soy in Preventing and Treating Chronic Disease, February 20-23, 1994, Mesa, AZ, p. 13-4, 1994.

DT (MEETING ABSTRACT)

FS ICDB

LA English

EM 199507

AB Although data from epidemiologic studies of cancer models suggest that genistein plays an important role in cancer prevention, the biochemical target(s) of genistein action is (are) not known. Genistein is a potent in vitro inhibitor of protein tyrosine kinase (PTK) activity, especially that of the epidermal growth factor receptor (EGF-R), having little effect on serine/threonine kinases. This led to the suggestions that genistein might exert its anticancer effects through inhibiting the activity of EGF-R PTK, or other crucial PTKs in vivo. Subsequent studies on intact tumor cell lines demonstrated that EGF-R and other growth factor receptors are able to transmit mitogenic signals in the presence of genistein. In fact, it is difficult to detect decreases in the tyrosine phosphorylation of discrete proteins after genistein treatment. Other mechanisms for the effect of genistein have been suggested from in vitro and cell culture data. Genistein not only inhibits the activity of purified topoisomerase II in vitro, but also leads to the accumulation of protein-associated single-strand breaks in whole cells. Genistein also inhibits the production of reactive oxygen species which may lead to tissue damage and DNA modification. Additionally, genistein acts as a weak estrogen, modifies cellular differentiation programs, inhibits angiogenesis, modulates cell cycle events and may precipitate apoptosis. However, few of the above mechanisms in tumor cells are sensitive to the physiologic serum concentrations of genistein (less than 5 ug/ml). Primary, nontransformed human mammary epithelial cells, which may have a much greater sensitivity

to genistein, would be a much better system for the study of these mechanisms.

CT Check Tags: Animal
Apoptosis: DE, drug effects
Cell Cycle: DE, drug effects
Cell Differentiation: DE, drug effects
DNA Topoisomerase (ATP-Hydrolysing): AI, antagonists & inhibitors
DNA, Neoplasm: DE, drug effects
Diet
Growth Inhibitors: PD, pharmacology
*Isoflavones: PD, pharmacology
Isoflavones: TU, therapeutic use
Neovascularization, Pathologic: PC, prevention & control
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
Protein-Tyrosine Kinase: ME, metabolism
Reactive Oxygen Species
Receptors, Epidermal Growth Factor-Urogastrone: AI, antagonists & inhibitors
Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism

RN 446-72-0 (Genistein)

CN EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 5.99.1.3 (DNA Topoisomerase (ATP-Hydrolysing)); 0 (DNA, Neoplasm); 0 (Growth Inhibitors); 0 (Isoflavones); 0 (Reactive Oxygen Species); 0 (Receptors, Epidermal Growth Factor-Urogastrone)

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L95	37	S	AG1478 OR AG 1478
L96	10	S	TYRPHOSTIN? (L) 1478
L97	2	S	L12
L98	37	S	L95-L97
L99	4	S	L98 AND APOPTOS?
		E	GAZIT A/AU
L100	133	S	E3,E6
		E	LEVITZKI A/AU
L101	261	S	E3-E5
		E	CAVENEE W/AU
L102	227	S	E3,E5-E7
		E	NAGANE M/AU
L103	28	S	E3,E5
		E	HUANG H/AU
L104	377	S	E3,E13-E15
L105	28643	S	APOPTOS?

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L106         29 S L105 AND TYRPHOSTIN?
L107      42934 S L19 OR CISPLATIN? OR VINCRISTIN? OR PACLITAXEL OR TAXOL
L108          0 S L98 AND L107
L109          6 S L100-L104 AND L98
L110         35 S L98 AND (DELTAEGF# OR EGF# OR EPIDERM?(L)GROW?)
L111         27 S L110 AND ?TYROSIN?
L112          4 S L100-L104 AND L111
L113          9 S L99,L109,L112
L114         22 S L111 NOT L113
L115          2 S L114 AND (GLIOM? OR LUNG)/TI
L116         11 S L113,L115
L117          7 S L110,L111 AND (LUNG OR BREAST OR GLIOM? OR OVAR?)
L118         14 S L116,L117

     FILE 'BIOSIS' ENTERED AT 09:06:19 ON 04 FEB 1999

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L118 ANSWER 1 OF 14  BIOSIS  COPYRIGHT 1999 BIOSIS
AN   1998:276403  BIOSIS
DN   PREV199800276403
TI   Inhibition of platelet-derived growth factor and
     epidermal growth factor receptor signaling events after
     treatment of cells with specific synthetic inhibitors of tyrosine
     kinase phosphorylation.
AU   Lipson, Kenneth E. (1); Pang, Long; Huber, L. Julie; Chen, Hui; Tsai,
     Jian-Ming; Hirth, Peter; Gazit, Aviv; Levitzki,
     Alexander; McMahon, Gerald
CS   (1) SUGEN Inc., 515 Galveston Dr., Redwood City, CA 94063 USA
SO   Journal of Pharmacology and Experimental Therapeutics, (May, 1998) Vol.
     285, No. 2, pp. 844-852.
     ISSN: 0022-3565.
DT   Article
LA   English
AB   The receptor kinase activity associated with the epidermal
     growth factor (EGF) receptor and platelet-derived
     growth factor (PDGF) receptor plays an important role in
     ligand-induced signaling events. The effect of specific, synthetic
     chemical inhibitors of PDGF- and EGF-mediated receptor
     tyrosine autophosphorylation on receptor signaling were examined
     in NIH 3T3 cells overexpressing PDGF or EGF receptors. Specific
     inhibition of ligand-dependent receptor autophosphorylation, PI3K
     activation,  mitogen-activated protein kinase (MAPK) activation, cyclin
     E-associated kinase activity and cell proliferation was measured after
     treatment of cells with these inhibitors. A synthetic PDGF receptor kinase
     inhibitor exhibited specific inhibitory properties when tested for
     PDGF-induced receptor autophosphorylation, MAPK activity, PI3K activation,
     entry into S phase and cyclin E-associated kinase activity. A synthetic
     EGF receptor kinase inhibitor showed selective inhibitory
     properties when tested  for EGF-induced receptor
     autophosphorylation, MAPK activation, PI3K activation, entry into S phase
     and cyclin E-associated kinase activity. In both cases, these compounds
     were found to be effective as inducers of growth arrest and
     accumulation of cells in the G1 phase of the cell cycle after ligand
     treatment. However, at high concentrations, the EGF receptor
     kinase inhibitor was observed to exhibit some nonspecific effects as
     demonstrated by attenuation of PDGF-induced receptor  autophosphorylation
     and cell cycle progression. This demonstrates that it is critical to use
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the lowest concentration of such an inhibitor that will alter the response under investigation, to have confidence that the conclusions derived from the use of such inhibitor are valid. We conclude that these experimental parameters signify useful end points to measure the relative selectivity of **tyrosine** kinase inhibitors that affect receptor-mediated signal transduction.

CC Pharmacology - General *22002
Cytology and Cytochemistry - Animal *02506
Biophysics - Membrane Phenomena *10508
Endocrine System - General *17002
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064

BC Muridae 86375

IT Major Concepts
Cell Biology; Pharmacology

IT Chemicals & Biochemicals
epidermal growth factor receptor; mitogen-activated protein kinase; platelet-derived **growth** factor receptor; **tyrosine** kinase; AG 1296: enzyme inhibitor - drug; **AG 1478**: enzyme inhibitor - drug

IT Miscellaneous Descriptors
signal transduction

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
NIH 3T3 (Muridae)

ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

RN 80449-02-1 (**TYROSINE** KINASE)
9026-43-1 (PROTEIN KINASE)

L118 ANSWER 2 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1998:264488 BIOSIS

DN PREV199800264488

TI Effect of **tyrosine** kinase inhibition on surfactant protein A gene expression during human **lung** development.

AU Klein, Jonathan M. (1); Dewild, Louis J.; McCarthy, Troy A.

CS (1) Dep. Pediatr., Univ. Iowa, 200 Hawkins Dr., Iowa City, IA 52242-1083 USA

SO American Journal of Physiology, (April, 1998) Vol. 274, No. 4 PART 1, pp. L542-L551.
ISSN: 0002-9513.

DT Article

LA English

AB **Epidermal growth** factor (**EGF**) stimulates surfactant protein (SP) A synthesis in human fetal **lung** explants. Ligand binding to the **EGF** receptor stimulates an intrinsic receptor **tyrosine** kinase with subsequent activation of second messengers. We hypothesized that inhibition of **EGF** -receptor **tyrosine** kinase activity would block SP-A expression in spontaneously differentiating cultured human fetal **lung** tissue. Midtrimester fetal **lung** explants were exposed for 4 days to genistein (a broad-range inhibitor of **tyrosine** kinases) and **tyrphostin AG-1478** (a specific inhibitor of **EGF**-receptor **tyrosine** kinase). Genistein significantly decreased SP-A and SP-A mRNA levels without affecting either tissue viability or the morphological differentiation of alveolar type II cells. **Tyrphostin AG-1478** also decreased SP-A content

and SP-A mRNA levels in cultured fetal **lung** explants. Treatment with **EGF** could not overcome the inhibitory effects of either genistein or **tyrphostin** on SP-A; however, only **tyrphostin** inhibited **EGF**-receptor **tyrosine** phosphorylation. We conclude that specific inhibition of **EGF** -receptor **tyrosine** kinase with **tyrphostin AG** **-1478** blocks the expression of SP-A during spontaneous differentiation of cultured human fetal **lung** tissue. Furthermore, exposure to genistein also decreases SP-A expression and blocks the effects of **EGF** in human fetal **lung** tissue without inhibiting **EGF**-receptor **tyrosine** phosphorylation. These findings support the importance of **tyrosine** kinase-dependent signal transduction pathways in the regulation of SP-A during human fetal **lung** development.

CC Respiratory System - Physiology and Biochemistry *16004
Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Biophysics - Membrane Phenomena *10508
Enzymes - Chemical and Physical *10806
Endocrine System - General *17002
Developmental Biology - Embryology - General and Descriptive *25502
Developmental Biology - Embryology - Morphogenesis, General *25508

BC Hominidae 86215

IT Major Concepts
Respiratory System (Respiration)

IT Parts, Structures, & Systems of Organisms
alveolar type II cells: respiratory system

IT Chemicals & Biochemicals
epidermal growth factor; **epidermal growth** factor receptors; mRNA [messenger RNA]; **tyrosine** kinase: inhibition

IT Miscellaneous Descriptors
lung development; signal transduction pathways; surfactant protein A gene expression

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae): fetus

ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

RN 80449-02-1 (**TYROSINE** KINASE)

L118 ANSWER 3 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1998:230911 BIOSIS

DN PREV199800230911

TI Preferential inhibition of glioblastoma cells with wild-type **epidermal growth** factor receptors by a novel **tyrosine** kinase inhibitor ethyl-2,5-dihydroxycinnamate.

AU Han, Yuchun; Caday, Cornelio G. (1); Umezawa, Kazuo; Nanda, Anil

CS (1) Dep. Neurosurgery, Louisiana State Univ. Med. Center, PO Box 33932, 1501 Kings Highway, Shreveport, LA 71130 USA

SO Oncology Research, (1997) Vol. 9, No. 11-12, pp. 581-587. ISSN: 0965-0407.

DT Article

LA English

AB **Epidermal growth** factor receptor (**EGFR**) gene overexpression and mutations play an important role in the pathogenesis of a variety of malignant human cancers. In this study, we tested the effects of a novel **EGFR tyrosine** kinase inhibitor,

ethyl-2,5-dihydroxycinnamate (EtDHC), against related human glioblastoma cell lines expressing specific forms of **EGFR** gene mutations. EtDHC more potently inhibited cell **growth** and DNA synthesis in glioblastoma cells with endogenous or overexpressed wild-type **EGFR** compared with those with truncated **EGFR**, by preferentially inhibiting the **tyrosine** kinase activity and autophosphorylation of the wild-type **EGFR**. Higher concentrations of EtDHC were required to inhibit cells expressing the truncated **EGFR**. These findings are the reverse of another highly specific **tyrosine** kinase inhibitor, **tyrphostin AG 1478**, which preferentially inhibited glioblastoma cells with truncated **EGFR** compared with those with wild-type **EGFR** . The differential susceptibility of various glioblastoma cells to highly specific **tyrosine** kinase inhibitors is significant because human **gliomas** are composed of heterogeneous cells with subsets of cells expressing specific gene mutations. This cellular heterogeneity could be one of the reasons why tumor cells are resistant to chemotherapy. Thus, EtDHC, especially when in combination with drugs targeting other specific gene mutations (such as **tyrphostin AG 1478**), holds a significant potential for chemotherapy for human glioblastomas.

CC Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Pathology, General and Miscellaneous - Therapy *12512
Nervous System - Pathology *20506
Pharmacology - Neuropharmacology *22024
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Biochemical Studies - General *10060
Enzymes - Methods *10804
Pharmacology - Clinical Pharmacology *22005
Tissue Culture, Apparatus, Methods and Media *32500

BC Hominidae 86215

IT Major Concepts
Pharmacology; Tumor Biology

IT Chemicals & Biochemicals
epidermal growth factor receptor; erbstatin: antineoplastic - drug; ethyl-2,5-dihydroxycinnamate: antineoplastic - drug, enzyme inhibitor - drug, pharmacodynamics, novel **tyrosine** kinase inhibitor; tyrphostin: antineoplastic - drug, **tyrosine** kinase inhibitor, enzyme inhibitor - drug

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
U87MG (Hominidae): human glioblastoma cells

ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

RN 80449-02-1 (**TYROSINE** KINASE)
100827-28-9 (ERBSTATIN)

L118 ANSWER 4 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1998:50046 BIOSIS

DN PREV199800050046

TI Role of heparin-binding EGF-related peptides in proliferation and **apoptosis** of activated ras-stimulated intestinal epithelial cells.

AU Zushi, Shinichiro (1); Shinomura, Yasuhisa; Kiyohara, Tatsuya; Miyazaki, Yoshiji; Tsutsui, Shusaku; Sugimachi, Masamitsu; Higashimoto, Yoshifumi; Kanayama, Shuji; Matsuzawa, Yuji

CS (1) Second Dep. Internal Med., Osaka Univ. Med. Sch., 2-2 Yamadaoka, Suita 565 Japan
SO International Journal of Cancer, (Dec. 10, 1997) Vol. 73, No. 6, pp. 917-923.
ISSN: 0020-7136.
DT Article
LA English
AB The ras mutation is a common and critical step in carcinogenesis. Autocrine growth factors are also known to play an important role in cancer cell growth and transformation. However, the contribution of autocrine growth factors in regulation of proliferation and **apoptosis** of activated ras-stimulated intestinal epithelium is not fully understood. Therefore, we constructed activated ras-transfected intestinal epithelial cell clones (IEC-ras) to examine the role of epidermal growth factor (EGF)-related peptides in the behavior of IEC-ras. Overexpression of EGF family growth factors (transforming growth factor alpha, heparin-binding EGF-like growth factor, amphiregulin and betacellulin) and stronger phosphorylation of the EGF receptor was observed in IEC-ras compared with control cells. IEC-ras proliferated more rapidly than control cells, and a specific EGF receptor kinase inhibitor, **AG1478**, abolished the increased proliferation of IEC-ras. Heparitinase and chlorate also prevented increased proliferation of IEC-ras. Additionally, IEC-ras expressed more bcl-2 and was more resistant to **apoptosis** induction by UV radiation and mitomycin C. **AG1478** suppressed bcl-2 expression and inhibited resistance to **apoptosis** of IEC-ras. Heparitinase and chlorate had effects similar to those of **AG1478**. Our data indicate that heparin-binding EGF family growth factors play an important role in both increased proliferation and resistance to **apoptosis** of ras-stimulated intestinal epithelial cells.
CC Neoplasms and Neoplastic Agents - General *24002
Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Biochemical Studies - General *10060
Enzymes - General and Comparative Studies; Coenzymes *10802
Digestive System - General; Methods *14001
Endocrine System - General *17002
Developmental Biology - Embryology - General and Descriptive *25502
BC Hominidae 86215
Muridae 86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Dental and Oral System (Ingestion and Assimilation); Tumor Biology
IT Chemicals & Biochemicals
amphiregulin: cellular overexpression; bcl-2: cellular expression; betacellulin: cellular overexpression; epidermal growth factor receptor: phosphorylation; heparin-binding epidermal growth factor: cellular overexpression; ras: mitogen, transfection; transforming growth factor-alpha: cellular overexpression; AGI478: enzyme inhibitor
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
HT-29 (Hominidae): human colon carcinoma cells; ICE-6 (Muridae): **apoptosis**, ras-transfected, proliferation, rat intestinal epithelial cells
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Rodents; Vertebrates

RN 117147-70-3 (AMPHIREGULIN)

L118 ANSWER 5 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:456427 BIOSIS
DN PREV199799755630
TI Radiation-induced proliferation of the human A431 squamous carcinoma cells is dependent on **EGFR tyrosine** phosphorylation.
AU Schmidt-Ullrich, R. K. (1); Mikkelsen, R. B.; Dent, P.; Todd, D. G.; Valerie, K.; Kavanagh, B. D.; Contessa, J. N.; Rorrer, W. K.; Chen, P. B.
CS (1) Dep. Radiation Oncol., Medical Coll. Virginia/Virginia Commonwealth Univ., PO Box 980058, Richmond, VA 23298-0058 USA
SO Oncogene, (1997) Vol. 15, No. 10, pp. 1191-1197.
ISSN: 0950-9232.
DT Article
LA English
AB Accelerated cellular repopulation has been described as a response of tumors to fractionated irradiation in both normal tissue and tumor systems. To identify the mechanisms by which cells enhance their proliferative rate in response to clinically used doses of ionizing radiation (IR) we have studied human mammary and squamous carcinoma cells which are autocrine **growth** regulated by the **epidermal growth** factor receptor (**EGFR**) and its ligands, transforming **growth** factor-alpha and **EGF**. Both **EGF** and IR induced **EGFR** autophosphorylation, comparable levels of phospholipase C-gamma activation as measured by inositol-1,4,5-triphosphate production, and as a consequence oscillations in cytosolic (Ca-2+). Activities of Raf-1 and mitogen-activated protein kinase (MAPK) were also stimulated by **EGF** and IR by Ca-2+-dependent mechanisms. All these responses to **EGF** and IR were dependent upon activation of **EGFR** as judged by the use of the specific inhibitor of **EGFR** autophosphorylation, tyrphostin **AG1478**. Importantly, IR-induced proliferation of A431 cells was also inhibited by **AG1478**. This is the first report which demonstrates a link between IR-induced activation of proliferative signal transduction pathways and enhanced proliferation. We propose that accelerated repopulation of tumors whose **growth** is regulated by **EGFR** is initiated by an IR-induced **EGFR** activation mechanism that mimics the effects of **growth** factors.
CC Cytology and Cytochemistry - Human *02508
Radiation - Radiation and Isotope Techniques 06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Lipids 10066
Enzymes - Physiological Studies *10808
Metabolism - Lipids *13006
Metabolism - Proteins, Peptides and Amino Acids *13012
Reproductive System - Pathology *16506
Endocrine System - General *17002
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Neoplasms and Neoplastic Agents - Biochemistry *24006
Neoplasms and Neoplastic Agents - Carcinogens and Carcinogenesis *24007
Tissue Culture, Apparatus, Methods and Media *32500
BC Hominidae *86215
IT Major Concepts
Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Metabolism; Oncology (Human Medicine, Medical Sciences); Radiation Biology; Reproductive System (Reproduction)
IT Chemicals & Biochemicals

TYROSINE; PHOSPHOLIPASE; INOSITOL-1,4,5-TRIPHOSPHATE; PROTEIN KINASE

IT Miscellaneous Descriptors
EPIDERMAL GROWTH FACTOR RECEPTOR; HUMAN **BREAST** CANCER CELL LINE; HUMAN VULVAR SQUAMOUS CELL CARCINOMA CELL LINE; INOSITOL-1,4,5-TRIPHOSPHATE; MITOGEN-ACTIVATED PROTEIN KINASE; PHOSPHOLIPASE C-GAMMA; RADIATION BIOLOGY; RADIATION-INDUCED PROLIFERATION; RAF-1 PROTEIN KINASE; TUMOR BIOLOGY; TUMOR CELL ACTIVATION; TUMOR CELL EXPRESSION; TUMOR CELL PRODUCTION; **TYROSINE** PHOSPHORYLATION

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
A-431 (Hominidae): cell line; MDA-MB-231 (Hominidae): cell line

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN 60-18-4 (**TYROSINE**)
9013-93-8 (PHOSPHOLIPASE)
88269-39-0 (INOSITOL-1,4,5-TRIPHOSPHATE)
9026-43-1 (PROTEIN KINASE)

L118 ANSWER 6 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:450438 BIOSIS
DN PREV199799749641
TI Unliganded **epidermal growth** factor receptor dimerization induced by direct interaction of quinazolines with the ATP binding site.
AU Arteaga, Carlos L. (1); Ramsey, Timothy T.; Shawver, Laura K.; Guyer, Cheryl A.
CS (1) Div. Med. Oncol., Vanderbilt Univ. Sch. Medicine, 1161 22nd Ave. South, 1956 TVC, Nashville, TN 37232-5536 USA
SO Journal of Biological Chemistry, (1997) Vol. 272, No. 37, pp. 23247-23254. ISSN: 0021-9258.
DT Article
LA English
AB Receptor dimerization is critical for signaling by the **epidermal growth** factor receptor (**EGFR**) **tyrosine** kinase. This occurs after binding of the receptor's extracellular domain by ligand or bivalent antibodies. The role of other receptor domains in dimerization is less clear, and there are no examples of dimers induced by direct perturbation of the **EGFR** kinase domain. Sub-micromolar concentrations of **AG-1478** and AG-1517, quinazolines specific for inhibition of the **EGFR** kinase, induced reversible receptor dimerization in vitro and in intact A431 cells. Consistent with the inhibitory effect of quinazolines on receptor kinase activity, the dimers formed lacked a detectable Tyr(P) signal. Quinazoline-induced **EGFR** dimerization was abrogated in vitro by ATP and the ATP analog adenyl-5'-yl imidodiphosphate. Receptors with a single-point mutation in the ATP binding site as well as wild-type **EGFR** with a covalent modification of the ATP site failed to dimerize in response to **AG-1478** and AG-1517. These data suggest that **EGFR** dimerization can be induced by the interaction of quinazolines at the ATP site in the absence of receptor ligand binding. In SKBR-3 cells, the quinazolines induced the formation of inactive **EGFR**/ErbB-2 heterodimers, potentially sequestering ErbB-2 from interacting with other coreceptors of the ErbB family. Structural studies of the quinazoline interaction with the **EGFR tyrosine** kinase domain should allow for an analysis of receptor-specific chemical features required for binding to the ATP site and disruption of signaling, a

strategy that can be perhaps applied to other tumor cell receptor systems.
CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Membrane Phenomena *10508
Enzymes - Chemical and Physical *10806
Endocrine System - General *17002
Neoplasms and Neoplastic Agents - Biochemistry *24006
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Membranes (Cell Biology); Oncology (Human Medicine, Medical Sciences)
IT Chemicals & Biochemicals
QUINAZOLINES; ATP; **TYROSINE** KINASE
IT Miscellaneous Descriptors
ATP; BINDING SITE; BIOCHEMISTRY AND BIOPHYSICS; CELL BIOLOGY; CELL SIGNALING; DIMERIZATION; **EPIDERMAL GROWTH** FACTOR RECEPTOR; HUMAN **BREAST** CANCER; INTERACTIONS; QUINAZOLINES; SKBR-3 CELL LINE; **TYROSINE** KINASE; UNLIGANDED; WILD-TYPE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 253-82-7D (QUINAZOLINES)
56-65-5Q (ATP)
42530-29-0Q (ATP)
94587-45-8Q (ATP)
111839-44-2Q (ATP)
80449-02-1 (**TYROSINE** KINASE)

L118 ANSWER 7 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:440915 BIOSIS
DN PREV199799740118
TI Inhibitors of epidermal growth factor receptor kinase and of cyclin-dependent kinase 2 activation induce growth arrest, differentiation, and **apoptosis** of human papilloma virus 16-immortalized human keratinocytes.
AU Ben-Bassat, Hannah; Rosenbaum-Mitrani, Stella; Hartzstark, Zippora; Shlomai, Zippora; Kleinberger-Doron, Nurit; **Gazit, Aviv**; Plowman, Gregory; Levitzki, Rubina; Tsvieli, Rimona; **Levitzki, Alexander (1)**
CS (1) Dep. Biol. Chem., Inst. Life Sci., Hebrew Univ. Jerusalem, Givat Ram, Jerusalem 91904 Israel
SO Cancer Research, (1997) Vol. 57, No. 17, pp. 3741-3750. ISSN: 0008-5472.
DT Article
LA English
AB Human papilloma virus 16 (HPV 16) is associated with cervical cancer and is therefore considered a major health risk for women. Immortalization of keratinocytes induced by HPV infection is largely due to the binding of p53 and Rb by the viral oncoproteins E6 and E7, respectively, and is driven to a large extent by a transforming growth factor alpha/amphiregulin epidermal growth factor receptor autocrine loop. In this study, we show that the growth of HPV 16-immortalized human keratinocytes can be blocked by a selective epidermal growth factor receptor kinase inhibitor, **AG 1478**, and by AG 555, a

blocker of cyclin-dependent kinase 2 (Cdk2) activation. **AG 1478** induces a massive increase in the Cdk2 protein inhibitors p27 and p21, whereas AG 555 appears to have a different mechanism of action, inhibiting the activation of Cdk2. Growth arrest induced by **AG 1478** and AG 555 is accompanied by up to 20% of cells undergoing **apoptosis**. Following **AG 1478** treatment but not AG 555 treatment, up to 50% of cells undergo terminal keratinocyte differentiation as determined by filaggrin expression and by the decline in the expression of cytokeratin 14. The growth-arresting properties of **AG 1478** and AG 555 identifies them as possible lead antipapilloma agents.

CC Cytology and Cytochemistry - Human *02508
Enzymes - Chemical and Physical *10806
Pathology, General and Miscellaneous - Necrosis *12510
Endocrine System - General *17002
Integumentary System - Physiology and Biochemistry *18504
Neoplasms and Neoplastic Agents - Biochemistry *24006
Developmental Biology - Embryology - Morphogenesis, General *25508
Genetics of Bacteria and Viruses *31500

BC Papovaviridae 02616
Hominidae *86215

IT Major Concepts
Cell Biology; Development; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Genetics; Integumentary System (Chemical Coordination and Homeostasis); Oncology (Human Medicine, Medical Sciences); Pathology

IT Chemicals & Biochemicals
KINASE

IT Miscellaneous Descriptors
ACTIVATION; **AG 1478**; AG 555; **APOPTOSIS**; CERVICAL CANCER; CYCLIN-DEPENDENT KINASE 2; DIFFERENTIATION; ENZYME INHIBITOR-DRUG; EPIDERMAL GROWTH FACTOR RECEPTOR KINASE; GROWTH ARREST; GROWTH-ARRESTING PROPERTY; HUMAN PAPILLOMAVIRUS-16; IMMORTALIZED; INTEGUMENTARY SYSTEM; KERATINOCYTE; NEOPLASTIC DISEASE; PHARMACODYNAMICS; REPRODUCTIVE SYSTEM DISEASE/FEMALE; TERMINAL DIFFERENTIATION; TUMOR BIOLOGY

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Papovaviridae: Viruses

ORGN Organism Name
human (Hominidae); Papovaviridae (Papovaviridae)

ORGN Organism Superterms
animals; chordates; humans; mammals; microorganisms; primates; vertebrates; viruses

RN 9031-44-1 (KINASE)

L118 ANSWER 8 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:403295 BIOSIS
DN PREV199799709498
TI Two- and three-dimensional cell structures govern epidermal growth factor survival function in human bladder carcinoma cell lines.
AU Dangles, Virginie; Femenia, Francoise; Laine, Veronique; Berthelemy, Madeleine; Le Rhun, Danielle; Poupon, Marie-France; Levy, Daniel; Schwartz-Cornil, Isabelle (1)
CS (1) URA-INRA-DGER d'Immunopathologie Cellulaire et Moleculaire, Ecole Nationale Veterinaire, 94704 Maisons Alfort cedex France
SO Cancer Research, (1997) Vol. 57, No. 16, pp. 3360-3364. ISSN: 0008-5472.
DT Article

LA English
AB Human bladder carcinomas often express high levels of the epidermal growth factor (EGF) receptor. In three human bladder carcinoma cell lines (OBR, T24, and 647V), we show that two EGF receptor ligands, namely EGF and transforming growth factor a, enhanced the **apoptosis** due to serum starvation on cells cultured as monolayers. Conversely, EGF and transforming growth factor a prevented **apoptosis** when the same serum-starved cells were cultured as three-dimensional spheroids. Both stimulation and inhibition of **apoptosis** by EGF were associated with p21 WAF1/CIP1 overexpression. In 647V spheroids, EGF protection against radiation-induced **apoptosis** was negated by genistein and tyrphostin **AG1478**, suggesting that blockade of the EGF signal transduction in patients with bladder cancer may improve the radiotherapy efficacy.
CC Cytology and Cytochemistry - Human *02508
Radiation - Radiation and Isotope Techniques 06504
Radiation - Radiation Effects and Protective Measures 06506
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Membrane Phenomena *10508
Pathology, General and Miscellaneous - Necrosis 12510
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - Proteins, Peptides and Amino Acids *13012
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies 15002
Urinary System and External Secretions - Pathology *15506
Endocrine System - General *17002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Endocrine System *22016
Pharmacology - Urinary System 22032
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Neoplasms and Neoplastic Agents - Biochemistry *24006
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy 24008
Tissue Culture, Apparatus, Methods and Media *32500
BC Hominidae *86215
IT Major Concepts
Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Membranes (Cell Biology); Metabolism; Oncology (Human Medicine, Medical Sciences); Pharmacology; Urology (Human Medicine, Medical Sciences)
IT Miscellaneous Descriptors
APOPTOSIS; CELL SURVIVAL FUNCTION; EPIDERMAL GROWTH FACTOR; HUMAN BLADDER CARCINOMA CELL LINE; OBR CELL LINE; P21 WAF1/CIP1 PROTEIN; THREE-DIMENSIONAL CELL STRUCTURE; TRANSFORMING GROWTH FACTOR-ALPHA; TUMOR BIOLOGY; TUMOR CELL EXPRESSION; TUMOR CELL OVEREXPRESSION; TWO-DIMENSIONAL CELL STRUCTURE; T24 CELL LINE; 647V CELL LINE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L118 ANSWER 9 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:365269 BIOSIS
DN PREV199799657202
TI Tyrphostin AG 494 blocks Cdk2 activation.
AU Osherov, Nir; **Levitzki, Alexander (1)**
CS (1) Dep. Biol. Chem., Alexander Wilverman Inst. Life Sci., Hebrew Univ.

Jerusalem, Givat Ram, Jerusalem 91904 Israel
SO FEBS Letters, (1997) Vol. 410, No. 2-3, pp. 187-190.
ISSN: 0014-5793.
DT Article
LA English
AB We have previously shown that the EGFR kinase selective **tyrphostin** AG 494 fails to inhibit EGFR kinase in intact cells. Yet, AG 494 proved to inhibit EGF- or serum-induced cell proliferation (Osherov et al., J. Biol. Chem. 268 (1993) 11134-11142). In this preliminary communication we show that AG 494 as well as its close analogs AG 490 and AG 555 block Cdk2 activation. In contrast, **AG 1478**, a more selective EGFR kinase blocker which is also active as EGFR kinase blocker in intact cells, fails to do so. AG 494 exerts its full inhibitory activity on Cdk2 activation even when added 20 h subsequent to EGF addition when Cdk2 activation is maximal. The inhibitory activity on Cdk2 activation parallels its DNA synthesis inhibitory activity, strongly suggesting that its target is one of the molecular mechanisms involved in Cdk2 activation. AG 494 and its analogs may become useful lead compounds for the development of drugs aimed at the cell cycle machinery.
CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
BC Muridae *86375
IT Major Concepts
Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Metabolism
IT Chemicals & Biochemicals
AG 494; KINASE
IT Miscellaneous Descriptors
ACTIVATION; AG 494; CDK2; DHER-14 CELL LINE; DNA; ENZYMOLOGY; EPIDERMAL GROWTH FACTOR RECEPTOR KINASE SELECTIVE TYRPHOSTIN; SYNTHESIS; TRANSFECTED NIH-3T3 CELLS
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN 133550-35-3 (AG 494)
9031-44-1 (KINASE)

L118 ANSWER 10 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:175003 BIOSIS
DN PREV199799466716
TI Inhibition of **tyrosine** kinase activity decreases expression of surfactant protein A in a human **lung** adenocarcinoma cell line independent of **epidermal growth** factor receptor.
AU Klein, Jonathan M. (1); McCarthy, Troy A.
CS (1) Dep. Pediatr., Univ. Iowa, 200 Hawkins Dr., Iowa City, IA 52242-1083 USA
SO Biochimica et Biophysica Acta, (1997) Vol. 1355, No. 3, pp. 218-230.
ISSN: 0006-3002.
DT Article
LA English
AB **Epidermal growth** factor (**EGF**) enhances fetal **lung** development in vivo and in vitro. Ligand binding to the

EGF receptor stimulates an intrinsic receptor **tyrosine** kinase initiating a signal transduction cascade. We hypothesized that blocking **EGF** receptor function with **tyrosine** kinase inhibitors would decrease the expression of surfactant protein A in human pulmonary epithelial cells. Human pulmonary adenocarcinoma cells (NCI-H441) were exposed to genistein (a broad range inhibitor of **tyrosine** kinases) and tyrphostin **AG1478** (a specific inhibitor of **EGF** receptor **tyrosine** kinase). Genistein significantly decreased surfactant protein A (SP-A) and SP-A mRNA levels in H441 cells without affecting cell viability. The inhibitory effect of genistein on SP-A content was reversible. In contrast, tyrphostin **AG1478** had no effect on SP-A levels despite a greater inhibitory effect than genistein on **EGF** receptor **tyrosine** autophosphorylation. Furthermore, treatment of H441 cells with exogenous **EGF** did not increase SP-A content or mRNA levels beyond baseline. We conclude that inhibition of **tyrosine** kinase activity other than the **EGF** receptor decreases the expression of surfactant protein A at a pretranslational level in human pulmonary adenocarcinoma cells. These results suggest the importance of **tyrosine** kinases in modulating human SP-A synthesis.

CC Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Membrane Phenomena *10508
Enzymes - Physiological Studies *10808
Respiratory System - Physiology and Biochemistry *16004

BC Hominidae *86215

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Membranes (Cell Biology); Respiratory System (Respiration)

IT Chemicals & Biochemicals
TYROSINE KINASE

IT Miscellaneous Descriptors
AUTOPHOSPHORYLATION; BIOSYNTHESIS; ENZYMOLOGY; **EPIDERMAL GROWTH** FACTOR RECEPTOR; EXPRESSION; HUMAN **LUNG** ADENOCARCINOMA CELL; INHIBITION; **LUNG** CELL LOCALIZATION; MEMBRANES; PRETRANSLATIONAL REGULATION; SIGNAL TRANSDUCTION; SIGNAL TRANSDUCTION COMPONENT; SURFACTANT PROTEIN A; SURFACTANT PROTEIN A GENE; SURFACTANT PROTEIN A SYNTHESIS MODULATOR; **TYROSINE** KINASE; **TYROSINE** KINASE ACTIVITY

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
NCI-H441 (Hominidae): cell line

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN 80449-02-1 (**TYROSINE** KINASE)

L118 ANSWER 11 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:152953 BIOSIS
DN PREV199799452156
TI EGF-R dependent regulation of keratinocyte survival.
AU Rodeck, Ulrich (1); Jost, Monika; Kari, Csaba; Shih, Daw-Tsun; Lavker, Robert M.; Ewert, Donald L.; Jensen, Pamela J.
CS (1) Wistar Inst., 3601 Spruce St., Philadelphia, PA 19104 USA
SO Journal of Cell Science, (1997) Vol. 110, No. 2, pp. 113-121. ISSN: 0021-9533.
DT Article

LA English
AB Tissue organization and maintenance within multicellular organisms is in part dependent on the ability of cells to undergo programmed cell death or **apoptosis**. Conversely, disruption of cell death pathways often is associated with tumor development. At present, the molecular control of **apoptosis** in epithelial cells is poorly understood. Here we describe evidence linking epidermal growth factor-receptor (EGF-R) activation to survival of normal human keratinocytes in culture. Inhibition of EGF-R activation by an anti-EGF-R antagonistic monoclonal antibody (mAb 425), followed by detachment of keratinocytes from the substratum, induced extensive death with several features of **apoptosis** in keratinocyte cultures. Other, non-epithelial normal human cells including melanocytes and fibroblasts, did not show this effect. Similar to EGF-R blockade by mAb 425, inhibition of the EGF-R tyrosine kinase activity using tyrphostin **AG1478** resulted in lack of attachment and extensive cell death upon passaging. Attachment to keratinocyte-derived ECM partially rescued mAb 425-treated keratinocytes from cell death, indicating that adhesion-dependent and EGF-R-dependent signal transduction pathways serve partially overlapping but not redundant roles in supporting keratinocyte survival.
CC Cytology and Cytochemistry - Human *02508
Biophysics - Membrane Phenomena *10508
Endocrine System - General *17002
BC Hominidae *86215
IT Major Concepts
Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Membranes (Cell Biology)
IT Chemicals & Biochemicals
INTEGRIN
IT Miscellaneous Descriptors
CELL BIOLOGY; EPIDERMAL GROWTH FACTOR RECEPTOR; EPIDERMAL GROWTH FACTOR-RECEPTOR DEPENDENT REGULATION; INTEGRIN-MEDIATED SUBSTRATE ADHESION; KERATINOCYTE SURVIVAL
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 153-87-7Q (INTEGRIN)
60791-49-3Q (INTEGRIN)

L118 ANSWER 12 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:490709 BIOSIS
DN PREV199699213065
TI Differential effects of **tyrphostin AG 1478** on human **glioma** cells expressing truncated or wild-type **EGFR**.
AU Han, Yuchun (1); Nanda, Anil (1); **Cavenee, Webster K.**; **Huang, H.-J. Su**; Caday, Cornelio G. (1)
CS (1) Neurosurg., La. State Univ. Med. Cent., 1501 Kings Highway, Shreveport, LA 71130 USA
SO Society for Neuroscience Abstracts, (1996) Vol. 22, No. 1-3, pp. 946.
Meeting Info.: 26th Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 16-21, 1996
ISSN: 0190-5295.
DT Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences,

Congresses, Review Annuals 00520
Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
Nervous System - Pathology *20506
Neoplasms and Neoplastic Agents - Biochemistry *24006
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Neurology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences)
IT Chemicals & Biochemicals
TYRPHOSTIN AG 1478; TYROSINE KINASE
IT Miscellaneous Descriptors
ENZYME INHIBITOR-DRUG; **EPIDERMAL GROWTH** FACTOR RECEPTOR; GENE TRUNCATION; HUMAN **GLIOMA** CELLS; MEETING ABSTRACT; MEETING POSTER; NERVOUS SYSTEM; OVEREXPRESSION; PATHOGENESIS; TUMOR BIOLOGY; **TYROSINE** KINASE; TYRPHOSTIN **AG1478**; U87MG CELL LINE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN **153436-53-4** (**TYRPHOSTIN AG 1478**)
80449-02-1 (**TYROSINE** KINASE)

L118 ANSWER 13 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:464733 BIOSIS
DN PREV199699187089
TI **Tyrphostin AG 1478** preferentially inhibits human **glioma** cells expressing truncated rather than wild-type **epidermal growth** factor receptors.
AU Han, Yuchun (1); Caday, Cornelio Gacusana; Nanda, Anil; **Cavenee, Webster K.; Huang, H.-J. Su**
CS (1) Dep. Neurosurg., Louisiana State Univ. Med. Cent., 1501 Kings Highway, Shreveport, LA 61130 USA
SO Cancer Research, (1996) Vol. 56, No. 17, pp. 3859-3861.
ISSN: 0008-5472.
DT Article
LA English
AB The effects of a new **epidermal growth** factor receptor (**EGFR**) **tyrosine** kinase inhibitor, **tyrphostin AG 1478**, were tested on three related human **glioma** cell lines: U87MG, which expressed endogenous wild-type (wt) **EGFR**, and two retrovirally infected U87MG cell populations which overexpressed either wt (U87MG.wtEGFR) or truncated **EGFR** (U87MG. DELTA-**EGFR**). Although **AG 1478** inhibited cell **growth**, DNA synthesis, **EGFR** **tyrosine** kinase activity, and receptor autophosphorylation of each cell line in a dose-dependent manner, it was significantly more potent in U87MG.DELTA-**EGFR** cells than in the other two cell lines. The increased inhibitory response of U87MG.DELTA-**EGFR** cells was due to a greater sensitivity of the constitutively autophosphorylated M-r 140,000 and 155,000 DELTA-**EGFR** species to **AG**

1478. These results suggest that **AG 1478** is a relatively specific inhibitor of the DELTA-**EGFR**, and this finding may have important therapeutic implications since the DELTA-**EGFR** occurs frequently in glioblastomas and in **breast**, **lung**, and **ovarian** cancers.

CC Cytology and Cytochemistry - Human 02508
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules 10506
Biophysics - Membrane Phenomena *10508
Enzymes - Chemical and Physical *10806
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Respiratory System - Pathology *16006
Reproductive System - Pathology *16506
Endocrine System - General *17002
Muscle - Pathology *17506
Nervous System - Pathology *20506
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Neoplasms and Neoplastic Agents - Biochemistry *24006

BC Hominidae *86215

IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Genetics; Membranes (Cell Biology); Metabolism; Muscular System (Movement and Support); Neurology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pulmonary Medicine (Human Medicine, Medical Sciences); Reproductive System (Reproduction)

IT Chemicals & Biochemicals
TYRPHOSTIN AG 1478; **TYROSINE** KINASE

IT Miscellaneous Descriptors
BREAST; DNA SYNTHESIS; GLIOBLASTOMA; **LUNG**; **OVARIAN** CANCER; PHOSPHORYLATION; **TYROSINE** KINASE

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
Hominidae (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN **153436-53-4** (**TYRPHOSTIN AG 1478**)
80449-02-1 (**TYROSINE** KINASE)

L118 ANSWER 14 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1995:60630 BIOSIS
DN PREV199598074930
TI **Epidermal-growth**-factor-dependent activation of the Src-family kinases.
AU Osherov, Nir; **Levitzki, Alexander (1)**
CS (1) Dep. Biol. Chem., Hebrew Univ. Jerusalem, Jerusalem 91904 Israel
SO European Journal of Biochemistry, (1994) Vol. 225, No. 3, pp. 1047-1053. ISSN: 0014-2956.
DT Article
LA English
AB The precise role of src-type kinases as signal transducers has been under intensive investigation but only in a few instances has their role been revealed in any detail. Thus, src, fyn and yes are activated upon stimulation by platelet-derived **growth** factor or

colony-stimulating factor in cells expressing high levels of these receptors. Activation of src-family kinases by other receptor **tyrosine** kinases such as the **epidermal-growth** -factor (**EGF**) receptor has not been directly demonstrated. In this report, we demonstrate **EGF**-dependent activation of src-family **tyrosine** kinases in NIH3T3 cells overexpresssing the human **EGF** receptor. Activation is rapid (lt 1 min) and persistent (up to 16 h). Furthermore, we show a correlation between the level of **EGF** receptor expressed and the degree of src-family kinase activation. We show that src-family kinase activity is also activated by addition of **EGF** to PC12 cells, which endogenously express relatively high levels of **EGF** receptor. Most strikingly, we show that A431 cells, which endogenously express very high levels of **EGF** receptor, show 10-fold elevated src-family kinase activity as compared to DHER14 cells, and that this activity is constitutive. This activity is completely blocked by **AG1478**, a specific inhibitor of the **EGF**-receptor **tyrosine** kinase activity, pointing to a direct link between overexpression of the **EGF** receptor and enhanced src-family kinase activity. Our findings suggest that **EGF** -dependent src-family kinase activity is detectable only when the levels of **EGF** receptor reach a specific level. Additionally, high levels of **EGF** receptor, as in A431 cells, may contribute to the elevated activation of src-family kinases. Sustained src-family kinase activation, similar to that seen in v-src-transformed cells, may play a role in tumorigenesis and tumor maintenance.

CC Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Animal 03506
Genetics and Cytogenetics - Human 03508
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
Endocrine System - General *17002
Neoplasms and Neoplastic Agents - Biochemistry *24006
Neoplasms and Neoplastic Agents - Carcinogens and Carcinogenesis *24007

BC Hominidae 86215
Muridae *86375

IT Major Concepts
Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Metabolism; Oncology (Human Medicine, Medical Sciences)

IT Chemicals & Biochemicals
EPIDERMAL-GROWTH-FACTOR; KINASES

IT Miscellaneous Descriptors
AG1478; NIH 3T3 CELL LINE; SIGNAL TRANSDUCTION; TUMOR MAINTENANCE; TUMORIGENESIS

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae); mouse (Muridae)

ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates

RN 62229-50-9 (**EPIDERMAL-GROWTH**-FACTOR)
9031-44-1D (KINASES)

=> fil uspat

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FILE 'USPATFULL' ENTERED AT 09:10:39 ON 04 FEB 1999
CA INDEXING COPYRIGHT (C) 1999 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 26 Jan 1999 (19990126/PD)
FILE LAST UPDATED: 27 Jan 1999 (19990127/ED)
HIGHEST PATENT NUMBER: US5864877
CA INDEXING IS CURRENT THROUGH 27 Jan 1999 (19990127/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 26 Jan 1999 (19990126/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: May 1998
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 1998

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>>> (IPC) Manuals, editions 1-6, in the /IC1, /IC2, /IC3, /IC4,     <<<
>>> /IC5, and /IC (/IC6) fields, respectively.  The thesauri in     <<<
>>> the /IC5 and /IC fields include the corresponding catchword     <<<
>>> terms from the IPC subject headings and subheadings.            <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> d his l120-


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L120           6 S L119 AND P/DT
                 SEL PN APPS
L121           0 S L120 NOT L43

     FILE 'WPIDS' ENTERED AT 09:08:15 ON 04 FEB 1999

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                 SEL L120 PN APPS

     FILE 'WPIDS' ENTERED AT 09:08:39 ON 04 FEB 1999
L122          10 S E68-E134

     FILE 'USPATFULL' ENTERED AT 09:08:54 ON 04 FEB 1999
L123           5 S (AG1478 OR AG 1478 OR TYRPHOSTIN? (L) 1478)/BI,AB,CT OR L12
                 SEL PN APPS

     FILE 'WPIDS' ENTERED AT 09:09:51 ON 04 FEB 1999
L124           8 S E135-E152
L125          10 S L122,L124
L126           0 S AG1478 OR AG 1478 OR TYRPHOSTIN? (L) 1478

     FILE 'USPATFULL' ENTERED AT 09:10:39 ON 04 FEB 1999

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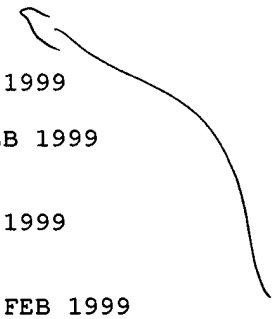

patents for AG 1478

L123 ANSWER 1 OF 5 USPATFULL
AN 1998:92048 USPATFULL
TI Methods and compositions for inhibiting cell proliferative disorders
IN Chen, Hui, Palo Alto, CA, United States
Gazit, Aviv, Jerusalem, Israel
Hirth, Klaus Peter, San Francisco, CA, United States
Mann, Elaina, Alameda, CA, United States
Shawver, Laura K., San Francisco, CA, United States
Tsai, Jianming, San Francisco, CA, United States
Tang, Peng Cho, Moraga, CA, United States
PA Sugen, Inc., Redwood City, CA, United States (U.S. corporation)
Yissum Research & Development Company of the Hebrew University of Jerusalem, Jerusalem, Israel (non-U.S. corporation)
PI US 5789427 980804
AI US 95-399967 950307 (8)
RLI Continuation-in-part of Ser. No. US 94-207933, filed on 7 Mar 1994, now abandoned
DT Utility
EXNAM Primary Examiner: Jordan, Charles T.; Assistant Examiner: Hardee, John R.
LREP Lyon & Lyon LLP
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 32 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 2892
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention concerns compounds and their use to inhibit the activity of a receptor tyrosine kinase. The invention is preferably used to treat cell proliferative disorders such as cancers characterized by over-activity or inappropriate activity HER2 or EGFR.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **153436-53-4P**
(receptor tyrosine kinase inhibitors, and prepn. thereof, for inhibiting cell proliferative disorders)

L123 ANSWER 2 OF 5 USPATFULL
AN 1998:75622 USPATFULL
TI Methods and compositions for inhibiting cell proliferative disorders
IN Chen, Hui, Palo Alto, CA, United States
Gazit, Aviv, Jerusalem, Israel
Levitzki, Alexander, Jerusalem, Israel
Hirth, Klaus Peter, San Francisco, CA, United States
Mann, Elaina, Alameda, CA, United States
Shawver, Laura K., San Francisco, CA, United States
Tsai, Jianming, San Francisco, CA, United States
Tang, Peng Cho, Moraga, CA, United States
PA Sugen, Inc., Redwood City, Israel (non-U.S. corporation)
Yissum Research and Development Company of the Hebrew University of Jerusalem, Jerusalem, Israel (non-U.S. corporation)
PI US 5773476 980630
AI US 95-486775 950607 (8)
RLI Continuation of Ser. No. US 95-399967, filed on 7 Mar 1995 which is a continuation-in-part of Ser. No. US 94-207933, filed on 7 Mar 1994, now abandoned
DT Utility
EXNAM Primary Examiner: Jordan, Charles T.; Assistant Examiner: Hardee, John R.

LREP Lyon & Lyon LLP
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN 32 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 2872
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention concerns compounds and their use to inhibit the activity of a receptor tyrosine kinase. The invention is preferably used to treat cell proliferative disorders such as cancers charcterized by over-activity or inappropriate activity HER2 or EGFR.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **153436-53-4P**
(receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

L123 ANSWER 3 OF 5 USPATFULL
AN 1998:7076 USPATFULL
TI Aryl and heteroaryl quinazoline compounds which inhibit EGF and/or PDGF receptor tyrosine kinase
IN Myers, Michael R., Reading, PA, United States
Spada, Alfred P., Lansdale, PA, United States
Maguire, Martin P., Mont Clare, PA, United States
Persons, Paul E., King of Prussia, PA, United States
PA Rhone-Poulenc Rorer Pharmaceuticals Inc., Collegeville, PA, United States (U.S. corporation)
PI US 5710158 980120
AI US 94-229886 940419 (8)
RLI Continuation-in-part of Ser. No. US 93-166199, filed on 23 Dec 1993, now patented, Pat. No. US 5480883 which is a continuation-in-part of Ser. No. US 92-988515, filed on 10 Dec 1992, now abandoned which is a continuation-in-part of Ser. No. US 91-698420, filed on 10 May 1991, now abandoned
DT Utility
EXNAM Primary Examiner: Dees, Jose G.; Assistant Examiner: Cebulak, Mary C.
LREP Parker, III, Raymond S.; Nicholson, James A.; Savitzky, Martin F.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1107
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to the modulation and/or inhibition of cell signaling, cell proliferation, cell inflammatory response, the control of abnormal cell growth and cell reproduction. More specifically, this invention relates to the use of mono- and/or bicyclic aryl or heteroaryl quinazoline compounds in inhibiting cell proliferation, including compounds which are useful protein tyrosine kinase (PTK) inhibitors. The method of treating cell proliferation using said quinazoline compounds and their use in pharmaceutical compositions is described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **153436-53-4**
(aryl and heteroaryl quinazoline compds. which inhibit EGF and/or PDGF receptor tyrosine kinase)

L123 ANSWER 4 OF 5 USPATFULL
AN 97:27169 USPATFULL
TI Quinazoline derivatives as anti-proliferative agents
IN Barker, Andrew J., Macclesfield, England

PA Zeneca Limited, London, United Kingdom (non-U.S. corporation)
PI US 5616582 970401
AI US 95-490666 950615 (8)
RLI Continuation of Ser. No. US 94-284293, filed on 2 Aug 1994, now patented, Pat. No. US 5457105 which is a continuation of Ser. No. US 93-5280, filed on 19 Jan 1993, now abandoned
PRAI GB 92-1095 920120
GB 92-13572 920626
GB 92-23735 921112
DT Utility
EXNAM Primary Examiner: Grumbling, Matthew V.
LREP Cushman Darby & Cushman Intellectual Property Group of Pillsbury Madison & Sutro, LLP
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3508
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention concerns quinazoline derivatives of the formula I ##STR1## wherein m is 1, 2 or 3 and each R.sup.1 includes hydroxy, amino, carboxy, carbamoyl, ureido, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, hydroxyamino, (1-4C)alkoxyamino, (2-4C)alkanoyloxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C)alkoxy and (1-3C)alkylenedioxy;

n is 1 or 2 and each R.sup.2 includes hydrogen, hydroxy, halogeno, trifluoromethyl, amino, nitro, cyano and (1-4C)alkyl; or a pharmaceutically-acceptable salt thereof;

processes for their preparation; pharmaceutical compositions containing them; and the use of the receptor tyrosine kinase inhibitory properties of the compounds in the treatment of cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **153436-53-4P**
(prepn. of, as tyrosine kinase-inhibiting anticancer agent)
IT **153436-53-4P**
(reactant, in prepn. of quinazoline anticancer agents)

L123 ANSWER 5 OF 5 USPATFULL
AN 95:90529 USPATFULL
TI Quinazoline derivatives useful for treatment of neoplastic disease
IN Barker, Andrew J., Macclesfield, England
PA Zeneca Limited, London, England (non-U.S. corporation)
PI US 5457105 951010
AI US 94-284293 940802 (8)
RLI Continuation of Ser. No. US 93-5280, filed on 19 Jan 1993, now abandoned
PRAI GB 92-1095 920120
GB 92-13572 920626
GB 92-23735 921112
DT Utility
EXNAM Primary Examiner: Shah, Mukund J.; Assistant Examiner: Grumbling, Matthew V.
LREP Cushman Darby & Cushman
CLMN Number of Claims: 29
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3702
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention concerns quinazoline derivatives of the formula I ##STR1## wherein m is 1, 2 or 3 and each R.sup.1 includes hydroxy, amino, carboxy, carbamoyl, ureido, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, hydroxyamino, (1-4C)alkoxyamino, (2-4C)alkanoyloxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C)alkoxy and (1-3C)alkylenedioxy;

n is 1 or 2 and each R.sup.2 includes hydrogen, hydroxy, halogeno, trifluoromethyl, amino, nitro, cyano and (1-4C)alkyl;

or a pharmaceutically-acceptable salt thereof;

processes for their preparation; pharmaceutical compositions containing them; and the use of the receptor tyrosine kinase inhibitory properties of the compounds in the treatment of cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **153436-53-4P**
(prepn. of, as tyrosine kinase-inhibiting anticancer agent)
IT **153436-53-4**
(reactant, in prepn. of quinazoline anticancer agents)

=> fil wpids

FILE 'WPIDS' ENTERED AT 09:11:06 ON 04 FEB 1999
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=> d all tot l125

L125 ANSWER 1 OF 10 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-557150 [47] WPIDS
DNN N98-434290 DNC C98-166731
TI Reporter system useful for analysis of protein-protein interactions - comprises first low affinity reporter sub-unit coupled to first putative binding group and second low affinity reporter sub-unit.
DC B04 D16 S03
IN BLAU, H M; MOHLER, W; ROSSI, F
PA (STRD) UNIV LELAND STANFORD JUNIOR
CYC 20
PI WO 9844350 A1 981008 (9847)* EN 71 pp G01N033-53 <--
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP
ADT WO 9844350 A1 **WO 98-US6648 980402**
PRAI US 98-53614 980401; **US 97-42576 970402; US 97-54638 970804**
IC ICM G01N033-53

ICS C12P021-06; G01N033-573

AB WO 9844350 A UPAB: 990122

Reporter system (RS) component comprises a first low affinity reporter subunit (LRS) coupled to a first putative binding group (PBM). The LRS is capable of associating with at least a second LRS to generate a detectable signal. This association is mediated by the PBM. Also claimed are: (1) a nucleic acid encoding a fusion protein (FP); (2) a viral vector comprising the nucleic acid of (1); (3) a cell transformed by the nucleic acid of (1), and (4) a method for determining the occurrence of binding between first and second PBMs which comprises: (a) providing a RS comprising a first LRS coupled to a fist PBM and second LRS coupled to a second PBM, where the first LRS can associate with at least one second LRS to generate a detectable signal, when the first and the second PBM bind together; (b) combining the first and second component, and (c) detecting the presence or absence of the signal.

The first PBM is preferably a protein comprising a signal transduction cascade, cell surface receptors, proteins regulating apoptosis, proteins that regulate progression of the cell cycle, proteins involved in the development of tumours, transcriptional regulatory proteins, translational regulatory proteins, proteins that affect cell interactions, cell adhesion molecules, proteins that are members of ligand-receptor pairs, proteins that precipitate in the folding of other proteins and proteins involved in targetting intracellular compartments. The first PBM can also be a drug, peptide or synthetic analogue.

USE - The RS is used for detecting, assaying and quantitating molecular interactions within living cells and in vitro, through complementation between at most 2 low-affinity RS, such as distinct Escherichia coli lacZ mutations. The method provides localisation of specific binding interactions within cells at different stages of development and differentiation, and an analysis of the induction or inhibition of binding interactions in cells.

ADVANTAGE - The process allows the study of protein-protein interactions and their control in living mammalian, especially human, cells without reliance upon the transcriptional activation of a reporter gene construct. Association of the proteins of interest results directly in enzyme activity and is independent of cellular functions. The method allows the detection of complexes excluded from the nucleus and detection of complexes whose formation would inhibit transcription.

Dwg.0/9

FS CPI EPI

FA AB

MC CPI: B04-N02; B12-K04; D05-H09; D05-H12C; D05-H12E; D05-H14; D05-H17C
EPI: S03-E14H4

L125 ANSWER 2 OF 10 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD

AN 98-465990 [40] WPIDS

CR 95-336717 [43]; 98-387069 [33]

DNC C98-141278

TI New acrylonitrile derivatives are EFGR and HER2 inhibitors - useful for treatment of cell proliferation disorders e.g. cancer, glioblastoma, blood vessel proliferative disorders and fibrotic disorders.

DC B05

IN CHEN, H; GAZIT, A; HIRTH, K P; MANN, E; SHAWVER, L K; TANG, P C; TSAI, J

PA (SUGE-N) SUGEN INC; (YISS) YISSUM RES & DEV CO

CYC 1

PI US 5789427 A 980804 (9840)* 41 pp A01N043-40 <--

ADT US 5789427 A **CIP of US 94-207933 940307, US 95-399967 950307**

PRAI **US 95-399967 950307; US 94-207933 940307**

IC ICM A01N043-40
ICS C07D211-72
AB US 5789427 A UPAB: 981008
Acrylonitrile derivatives of formula (I) and their salts are new. R1-R3 = alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, OH, NH2, thioether, SH, halo, H, NO2 or amine; Y = C(CN)=CH, alkyl, NH-alkyl or is absent; R5 = CN or aryl; provided that if R5 = phenyl, R1-R3 are not alkoxy or OH and that at least one of R1-R3 is not H.
USE - (I) are used for the treatment of cell proliferation disorders, especially those characterised by inappropriate EGFR activity or over activity of HER2. Such disorders include breast carcinoma, stomach, salivary gland and ovarian adenocarcinomas, endometrial cancer, gastric cancer, colorectal cancer and glioblastoma (claimed). (I) are also useful for the treatment of blood vessel proliferative disorders and fibrotic disorders e.g. psoriasis and to diagnose activity of a particular receptor tyrosine kinase.
ADVANTAGE - (I) are selective for EFGR-kinase and HER2.
Dwg.0/7
FS CPI
FA AB; DCN
MC CPI: B10-A08; B10-A10; B14-F01; B14-H01; B14-H01B; B14-N17C

L125 ANSWER 3 OF 10 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-387069 [33] WPIDS
CR 95-336717 [43]; 98-465990 [38]
DNC C98-117039
TI Amide derivatives are HER-2 inhibitors - useful for treatment of cell proliferative disorders, e.g. breast carcinoma(s), stomach adenocarcinoma(s) and glioblastoma(s).
DC B05
IN CHEN, H; GAZIT, A; HIRTH, K P; LEVITZKI, A; MANN, E; SHAWVER, L K; TANG, P C; TSAI, J
PA (SUGE-N) SUGEN INC; (YISS) YISSUM RES & DEV CO
CYC 1
PI US 5773476 A 980630 (9833)* 39 pp A01N037-18 <--
ADT US 5773476 A **CIP of US 94-207933 940307, Cont of US 95-399967 950307, US 95-486775 950607**
PRAI **US 95-399967 950307; US 94-207933 940307; US 95-486775 950607**
IC ICM A01N037-18
AB US 5773476 A UPAB: 981008
Amide derivatives of formula (I) and their salts are new. R1-R3 = R, alkoxy or OH; R = alkyl, alkenyl, alkynyl, alkylaryl, halogen, H, amine, thioether, SH or NH2; R6 = R; and X1-X5 = H, halogen, trihalomethyl, alkyl, alkenyl, alkynyl, alkoxy or NO2; provided that at least one of X1-X5 = trihalomethyl.
USE - (I) are inhibitors of HER-2 activity, useful for treatment of cell proliferative disorders, particularly a disease characterised by inappropriate epidermal growth factor receptor (EGFR) activity or cancer, especially breast carcinomas, stomach adenocarcinomas, salivary gland adenocarcinomas, endometrial cancers, ovarian adenocarcinomas, gastric cancers, colorectal cancers and glioblastomas (claimed). (I) may also be used in the treatment of blood vessel proliferative disorders and fibrotic disorders. (I) can also be used in the diagnosis of cancer. Administration is intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical or transmucosal. Dosage is 0.02-25 (preferably 0.02-15, especially 0.2-15) mg/kg/day.
Dwg.0/7
FS CPI

FA AB; GI; DCN
MC CPI: B10-A15; B12-K04A1; B14-F02; B14-H01B

L125 ANSWER 4 OF 10 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-260963 [23] WPIDS
DNC C98-080953
TI Preparation of mono-, hetero- or poly-cyclic fused pyrimidone ring compounds - used in treating hyperproliferative skin disorders e.g. psoriasis, papilloma virus and skin cancer.
DC B02
IN HIRTH, K P; MCMAHON, G; NAROG, B; SHAWVER, L K; TANG, P C
PA (SUGE-N) SUGEN INC
CYC 77
PI WO 9810767 A2 980319 (9823)* EN 118 pp A61K031-505 <--
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9743429 A 980402 (9833) A61K031-505 <--
ADT WO 9810767 A2 **WO 97-US16145 970911**; AU 9743429 A **AU 97-43429 970911**
FDT AU 9743429 A Based on WO 9810767
PRAI **US 97-48372 970603; US 96-26067 960913; US 96-31436 961120; US 97-34981 970108**
REP No-SR.Pub
IC ICM A61K031-505
AB WO 9810767 A UPAB: 980610
The following are claimed: (A) Preparation of a substituted pyrimidone fused ring system (II), either monocyclic, polycyclic or heterocyclic by reacting a beta -aminoacrylic acid precursor (I) with formamidine or its salt. (B) Treatment of a hyperproliferative skin disorder, by administering any of the following quinazolines: 4-(3-bromophenylamino)-6,7-dimethoxyquinazoline (Ia); 4-(3-chlorophenylamino)-6,7-dimethoxyquinazoline ; 4-(3-chlorophenylamino)-6-methylquinazoline; 4-(3-trifluoromethylphenylamino)-6-methylquinazoline; 4-(3-trifluoromethylphenylamino)-6,7-dimethoxyquinazoline; and 4-(3-cyanophenylamino)-6,7-dimethoxyquinazoline. (C) Preparation of a 4-halopyrimidine (III), by reacting a pyrimidone (II) with a halogenating agent, and isolating or purifying by precipitation, crystallisation, or sublimation. (D) Preparation of a 4-arylaminopyrimidine (IV) as hydrochloride salt, comprising: (a) dissolving a substituted aniline in ethanol; (b) adding a chloropyrimidine (III) and reacting; and (c) isolating (IV) as hydrochloride salt. (E) Preparation of (IV) base, comprising the steps (a) and (b) in (D), then either adding an alkali and isolating (IV) base; or adding step (c), dissolving the salt in alkali and isolating (IV) base. (F) Preparation of a topical formulation mixing quinazoline or its derivatives or salts with a non-polar hydrocarbon mixture to form a dispersion, then mixing with a penetration enhancer.

USE - The hyperproliferative skin disorders include psoriasis in its various forms, papilloma virus infection, seborrhoeic keratoses, acanthosis nigricans, ichthyosis, keratodermias, genodermatoses, Darier's disease, lichen planus, pityriasis rubra pilaris, and skin cancers, either basal or squamous cell type, or melanoma.

ADVANTAGE - In (A), the reaction can be run at a lower, more convenient, operating temperature, and with improved yield, by using formamidine or its salt rather than the traditional formamide. In (C), reagents and conditions are chosen to provide better yields and purity

than prior art e.g. 4-chloro-6,7-dimethoxyquinazoline is obtained in 89% yield, against 29% previously. Chromatographic purification is not required. In (D), denatured ethanol is used in place of conventional isopropanol. In (E), the crude reaction mixture can be basified directly to obtain (IVA) base, thus simplifying the process.
Dwg.0/4
FS CPI
FA AB; DCN
MC CPI: B06-D06; B07-D12; B14-H01; B14-N17

L125 ANSWER 5 OF 10 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-042831 [04] WPIDS
CR 92-415666 [50]; 95-231238 [30]
DNC C97-013564
TI Admin. of aryl and hetero-aryl quinazoline cpds. having protein kinase activity - for selective treatment of cell growth and differentiation characterised by activity of the human epidermal growth factor receptor type 2.
DC B02
IN MAGUIRE, M P; MYERS, M R; PERSONS, P E; SPADA, A P
PA (RHON) RHONE POULENC RORER PHARM INC; (RHON) RHONE-POULENC RORER PHARM INC
CYC 71
PI WO 9639145 A1 961212 (9704)* EN 33 pp A61K031-535
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BB BG BR BY CA CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
AU 9661044 A 961224 (9715) A61K031-535
US 5721237 A 980224 (9815) 10 pp A61K031-505
CZ 9703503 A3 980318 (9817) A61K031-535
EP 831831 A1 980401 (9817) EN A61K031-535
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
SK 9701663 A3 980603 (9834) A61K031-535
AU 696456 B 980910 (9848) A61K031-535
ADT WO 9639145 A1 WO 96-US9606 960606; AU 9661044 A AU 96-61044 960606; US 5721237 A **CIP of US 91-698420 910510, CIP of US 92-988515 921210, CIP of US 93-166199 931210, CIP of WO 94-US14180 941208**, US 95-469147 950606; CZ 9703503 A3 WO 96-US9606 960606, CZ 97-3503 960606; EP 831831 A1 EP 96-918362 960606, WO 96-US9606 960606; SK 9701663 A3 WO 96-US9606 960606, SK 97-1663 960606; AU 696456 B AU 96-61044 960606
FDT AU 9661044 A Based on WO 9639145; US 5721237 A CIP of US 5480883; CZ 9703503 A3 Based on WO 9639145; EP 831831 A1 Based on WO 9639145; AU 696456 B Previous Publ. AU 9661044, Based on WO 9639145
PRAI US 95-469147 950606; **US 91-698420 910510; US 92-988515 921210; US 93-166199 931210; WO 94-US14180 941208**
REP US 5480883
IC ICM A61K031-505; A61K031-535
ICS A61K031-495; A61K031-50; C07D235-02; C07D403-04
AB WO 9639145 A UPAB: 980309
Selective treatment of cell growth and differentiation characterised by activity of the human epidermal growth factor receptor type 2 (HER2) comprises admin. of aryl and heteroaryl quinazoline cpds. of formula (I) or their salts. A = mono- or bi-cyclic aryl, heteroaryl, cycloalkyl or heterocycloalkyl ring system having 5-12 atoms; X = bond, O, S, SO, SO2, OCH2, CR4=CR4, C triple bond C, NR4 or NR4CH2; R = H, alkyl, Ph, halophenyl, aralkyl, OH, alkoxy, aryloxy, acyloxy, halo, haloalkyl, amino,

mono- or di-alkylamino, acylamino, carboxy, amido, mono- or di-alkylamido, alkylthio, alkylsulphinyl or alkylsulphonyl; R4 = H, alkoxy or aralkoxy; and R5-R8 = H, alkoxy or aralkoxy. Also claimed are: 6,7-dimethoxy-4-(alpha -naphthylamino)quinazoline (Ia); and 4-(1-benzylindol-3-yl)-6,7-dimethoxy quinazoline (Ib).

USE - (I) have selective inhibition of HER2 autophosphorylation properties.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B06-D06; B14-D06; B14-E11

L125 ANSWER 6 OF 10 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 95-336717 [43] WPIDS
CR 98-387069 [33]; 98-465990 [38]
DNC C95-148432
TI Use of new and known protein kinase inhibitors - in treatment of cell proliferative disorders such as cancers.
DC B02 B05
IN CHEN, H; GAZIT, A; HIRTH, K P; LEVITZKI, A; MANN, E; SHAWVER, L K; TANG, P C; TSAI, J
PA (SUGE-N) SUGEN INC; (YISS) YISSUM RES & DEV CO
CYC 61
PI WO 9524190 A2 950914 (9543)* EN 122 pp A61K031-275 <--
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NL NO NZ PL PT RO RU SD SE SG SI SK TJ TT UA UZ VN
AU 9520968 A 950925 (9601) <--
WO 9524190 A3 951109 (9621) <--
ADT WO 9524190 A2 **WO 95-US2826 950306**; AU 9520968 A **AU 95-20968 950306**
FDT AU 9520968 A Based on WO 9524190
PRAI **US 94-207933 940307**
REP 4.Jnl.Ref ; EP 537742; EP 566226
IC ICM A61K031-275
ICS A61K031-495; C07C255-34; C07C311-13; C07C317-14; C07C327-44; C07D241-52
AB WO 9524190 A UPAB: 981008
Protein kinase inhibitor compsn. comprises cpd. of formula (I), (II), (III) or (IV). In (I), R1-R3 are alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, OH, amine, thioether, SH, halo, H, NO2 or NH2; R5 is alkylaryl comprising an alkyl gp. and aryl gp. of formula (i); X1-X5 are H, halo, alkyl, trihaloethyl or NO2; In (II), R1 and R3 are alkyl, alkenyl, alkynyl, alkoxy or alkylaryl; R4 is alkyl, alkylaryl, thioamide or amide; In (III), R1, R2, R5 and R6 are alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, halo, H, OH, amino; thioether, SH or NH2; X1-X5 are H, halo, trihalomethyl, alkyl, alkenyl, alkynyl, alkoxy or NO2; provided that at least one of X1-X5 is trihalomethyl; In (IV), R7-R10 are alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, OH, NO2, amine thioether, SH, halo, H or NH2; R12 is C(=X6)X7; X6 is O or S; X7 is Me or trihalomethyl; R13 is aryl or alkylaryl.

USE - Used for inhibition of EGFR and/or HER2 activity and esp. for treatment of cell proliferative disorders such as cancers. Admin. is, e.g. 0.02-25 (esp. 0.2-15) mg/kg/day.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B06-D05; B06-D06; B06-D18; B10-A08; B10-A09C; B10-A15; B14-D06;

B14-H01B

L125 ANSWER 7 OF 10 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 95-231238 [30] WPIDS
CR 92-415666 [50]; 97-042831 [04]
DNC C95-106691
TI Tyrosine kinase inhibitor compsn. for treating bone diseases and inflammation - contains cpd. having bis ring system comprising aryl ring and aryl-, carbocyclic- or heterocyclic- ring.
DC B02
IN HSU, C J; JOHNSON, S E; MAGUIRE, M P; MYERS, M R; PERSONS, P E; SPADA, A P; ZILBERSTEIN, A
PA (RHON) RHONE POULENC RORER PHARM INC; (RHON) RHONE-POULENC RORER PHARM INC
CYC 58
PI WO 9515758 A1 950615 (9530)* EN 38 pp A61K031-505 <--
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK ES FI GB GE HU JP KE KG KP KR KZ LK LT LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA US UZ VN
AU 9513050 A 950627 (9541) A61K031-505 <--
US 5480883 A 960102 (9607) 32 pp A61K031-495 <--
US 5646153 A 970708 (9733) 35 pp A61K031-505
US 5710158 A 980120 (9810) 19 pp A61K031-505 <--
US 5714493 A 980203 (9812) 18 pp A61K031-505 <--
US 5795889 A 980818 (9840) A61K031-47
EP 871448 A1 981021 (9846) EN A61K031-505 <--
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
ADT WO 9515758 A1 **WO 94-US14180 941208**; AU 9513050 A **AU 95-13050 941208**; US 5480883 A **CIP of US 91-698420 910510, CIP of US 92-988515 921210, US 93-166199 931210**; US 5646153 A **CIP of US 91-698420 910510**, CIP of WO 92-US3736 920506, **CIP of US 92-988515 921210, Div ex US 93-166199 931210**, US 95-439027 950511; US 5710158 A **CIP of US 91-698420 910510**, CIP of WO 92-US3736 920506, **CIP of US 92-988515 921210, CIP of US 93-146072 931108, CIP of US 93-166199 931210, US 94-229886 940419**; US 5714493 A **CIP of US 91-698420 910510, CIP of US 92-988515 921210, CIP of US 93-166199 931210, CIP of US 94-229886 940419, WO 94-US14180 941208, US 96-652444 960604**; US 5795889 A **CIP of US 91-698420 910510**, CIP of WO 92-US3736 920506, **CIP of US 92-988515 921210, Div ex US 93-166199 931210**, US 95-386271 950209; EP 871448 A1 **WO 94-US14180 941208, EP 95-904308 941208**
FDT AU 9513050 A Based on WO 9515758; US 5646153 A Div ex US 5480883; US 5710158 A CIP of US 5409930, CIP of US 5480883; US 5714493 A CIP of US 5480883, Based on WO 9515758; US 5795889 A Div ex US 5480883; EP 871448 A1 Based on WO 9515758
PRAI **US 94-229886 940419; US 93-166199 931210; US 91-698420 910510; US 92-988515 921210**; WO 92-US3736 920506; US 95-439027 950511; **US 93-146072 931108; US 96-652444 960604**; US 95-386271 950209
REP 1.Jnl.Ref ; EP 520722; EP 566226; EP 602851; US 3470182; US 3551427; US 3772295; US 3800039; US 4343940; US 4464375; WO 9220642
IC ICM A61K031-47; A61K031-495; A61K031-505
ICS A61K031-38; A61K031-44; A61K031-535; C07D215-16; C07D239-72; C07D239-74; C07D239-88; C07D239-93; C07D239-94; C07D241-04; C07D241-52; C07D241-54; C07D265-28; C07D319-18; C07D333-06
AB WO 9515758 A UPAB: 990107
Tyrosine kinase (TK) inhibitor compsn., for inhibiting colony stimulating

factor 1 receptor (CSF-1R) TK activity, by inhibiting of cell proliferation and/or differentiation and/or mediator release, comprises a cpd. having a bis ring system contg. a first aryl ring and a second aryl, carbocyclic or heterocyclic ring, or its salt, in admixt. with a carrier. Also claimed are cpds. with the activity above which are aryl- and heteroaryl-quinazoline cpds. of formula (I) and their salts: Ar = a 5-12 atom mono- or bi-cyclic aryl or heteroaryl system contg. 0-3 atoms from N, O and S in a mono- and 0-4 in a bi- cyclic system, provided that O-O, S-S, and O-S bonds are excluded, and opt. substd. by 0-3 of R; R = H, alkyl, alkenyl, phenyl, aralkyl, aralkenyl, OH, hydroxyalkyl, alkoxy, alkoxyalkyl, aralkoxy, aryloxy, acyloxy, halo, haloalkyl, nitro, cyano, amino, mono- and di-alkylamino, acylamino, COOH, carboxyalkyl, carboalkoxy, carbaralkoxy, carbalkoxyalkyl, carbalkoxyalkenyl, aminoalkoxy, amido, mono- and di-alkylamido, N,N-cycloalkylamido, sulphonyl, mono- and di-alkylsulphonyl, sulphamoyl, mono- and di-alkylsulphamoyl, halophenyl, or benzoyl; or two adjacent R = oxo; X = a bond, O, S, SO, SO2, OCH2, C=C, C triple bond C, C=S, SCH2, NH, NHCH2, NR4, or NR4CH2; R4 = alkyl, CH2, or CH2CH2CH2; and R5-R7 = H, alkyl, alkylthio, cycloalkyl, OH, alkoxy, aralkoxy, aryl, halo, haloalkyl, COOH, or carbalkoxy.

USE - (I) are used in treatment of bone diseases and inflammation (claimed) and also in treatment of psoriasis, atherosclerosis, and restenosis injuries and in studying CSF-1 receptor signalling in bone remodelling and haematopoeisis. The dosage of (I) is 0.01-100 mg/kg/day, orally or parenterally.

ADVANTAGE - (I) selectively inhibit differentiation, proliferation and mediator release.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B06-D07; B14-C03; B14-N01

L125 ANSWER 8 OF 10 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 93-281092 [36] WPIDS
DNC C93-125463
TI New 4-anilino quinazoline(s) with anti-cancer activity - are tyrosine kinase receptor inhibitors, useful against solid tumours, leukaemia, etc..
DC B02
IN BARKER, A J
PA (ZENE) ZENECA LTD
CYC 30

PI	AU 9331010	A	930722	(9336)*	109 pp	C07D239-74	<--
	HU 63153	T	930728	(9336)		C07D239-94	<--
	NO 9300178	A	930721	(9338)		C07D239-94	<--
	CA 2086968	A	930721	(9341)		C07D239-94	<--
	FI 9300208	A	930721	(9341)		C07D239-94	
	EP 566226	A1	931020	(9342) EN	64 pp	C07D239-94	<--
	R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE						
	ZA 9300015	A	930929	(9344)	109 pp	C07D000-00	<--
	CZ 9300043	A3	931013	(9350)		C07D239-94	
	JP 06073025	A	940315	(9415)	51 pp	C07D239-94	<--
	SK 9300016	A3	930909	(9419)		A61K031-505	
	AU 661533	B	950727	(9538)		C07D239-94	<--
	NZ 245662	A	950926	(9544)		C07D239-94	
	US 5457105	A	951010	(9546)	34 pp	A61K031-51	<--
	EP 566226	B1	951108	(9549) EN	72 pp	C07D239-94	<--
	R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE						
	DE 69300754	E	951214	(9604)		C07D239-94	
	ES 2078798	T3	951216	(9606)		C07D239-94	<--

TW 283146	A	960811 (9701)		C07D239-84		
US 5616582	A	970401 (9719)	35 pp	C07D403-00	<--	
CZ 282038	B6	970416 (9722)		C07D239-94	<--	
NO 301541	B1	971110 (9801)		C07D239-94		
CA 2086968	C	980623 (9836)		C07D239-94	<--	
MX 185311	B	970716 (9846)		C07D239-094		

ADT AU 9331010 A **AU 93-31010 930104**; HU 63153 T **HU 93-94 930115**; NO 9300178 A **NO 93-178 930119**; CA 2086968 A **CA 93-2086968 930108**; FI 9300208 A FI 93-208 930119; EP 566226 A1 **EP 93-300270 930115**; ZA 9300015 A **ZA 93-15 930104**; CZ 9300043 A3 **CZ 93-43 930118**; JP 06073025 A **JP 93-26577 930216**; SK 9300016 A3 SK 93-16 930119; AU 661533 B **AU 93-31010 930104**; NZ 245662 A NZ 93-245662 930112; US 5457105 A **Cont of US 93-5280 930119, US 94-284293 940802**; EP 566226 B1 **EP 93-300270 930115**; DE 69300754 E DE 93-600754 930115, **EP 93-300270 930115**; ES 2078798 T3 **EP 93-300270 930115**; TW 283146 A TW 93-100292 930118; US 5616582 A **Cont of US 93-5280 930119, Cont of US 94-284293 940802, US 95-490666 950615**; CZ 282038 B6 **CZ 93-43 930118**; NO 301541 B1 **NO 93-178 930119**; CA 2086968 C **CA 93-2086968 930108**; MX 185311 B MX 93-277 930120

FDT AU 661533 B Previous Publ. AU 9331010; DE 69300754 E Based on EP 566226; ES 2078798 T3 Based on EP 566226; US 5616582 A Cont of US 5457105; CZ 282038 B6 Previous Publ. CZ 9300043; NO 301541 B1 Previous Publ. NO 9300178

PRAI **GB 92-23735 921112**; **GB 92-1095 920120**; **GB 92-13572 920626**; GB 93-39 930104

REP 6.Jnl.Ref ; EP 520722; GB 2033894; GB 2160201; US 3985749; WO 9214716

IC ICM A61K031-51; C07D000-00; C07D239-094; C07D239-74; C07D239-84; C07D239-94; C07D403-00

ICS A61K031-495; A61K031-535; C07D239-72; C07D239-82; C07D401-02; C07D401-04; C07D403-02; C07D403-04; C07D403-06; C07D403-10; C07D413-02; C07D413-04; C07D413-06; C07D413-10; C07D413-12; C07D491-056

ICA A61K031-505; C07D403-12

ICI C07D239:00, C07D319:00, C07D491-056; C07D239:00, C07D317:00, C07D491-056; C07D239:00, C07D319:00, C07D491-056; C07D239:00, C07D317:00, C07D491-056; C07D239:00, C07D319:00, C07D491-056; C07D239:00, C07D317:00, C07D491-056

AB AU 9331010 A UPAB: 931122

4-Anilinoquinazolines of formula (I) and their salts are new. In (I), m is 1-3; n is 1-2; R2 is H, OH, halo, CF3, amino, nitro, CN, 1-4C alkyl, 1-4C alkoxy, mono- or di- (1-4C alkyl)amino, 1-4C alkylthio, 1-4C alkylsulphinyl or 1-4C alkylsulphonyl; R1 is e.g. OH, amino, carboxy, carbamoyl, ureido, 1-4C alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-((1-4C)alkyl)carbamoyl, hydroxyamino, (1-4C)alkoxyamino, (2-4C)alakanoyloxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C)alkoxy, (1-3C)alkylenedioxy, (1-4C)alkylamino, di((1-4C)alkyl)amino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-(1-4C)alkylpiperazin-1-yl, (1-4C)alkylthio, etc. and R2 is H, OH, halo, CF3, amino, nitro, CN, 1-4C alkyl, 1-4C alkylsulphonyl, 1-4C alkylsulphinyl, 1-4C alkylthio, or mono- or di-(1-4C alkyl)amino; except that (Q is quinazoline); 4-(4'-hydroxyanilino)- 6-methoxy-Q; 4-(4'-hydroxyanilino)- 6,7,8-trimethoxy-Q; 6-amino-4 -(4'-aminoanilino)-Q; and HCl salt, etc. are excluded.

USE - (I), and the excluded cpds., have tyrosine kinase receptor inhibitory properties giving rise to anti-cancer activity. They are expected to be active against cancers of the usual organs and against leukaemias, lymphoid malignancies, and solid tumours. Dosage is 1-50

mg/kg/day.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B06-D06; B12-G01B2; B12-G05; B12-G07

L125 ANSWER 9 OF 10 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 92-415666 [50] WPIDS
CR 95-231238 [30]; 97-042831 [04]
DNC C92-184451
TI Inhibiting cell proliferation with bis ring cpds. - e.g. 3-phenyl or thienyl quinoline derivs. which inhibit growth factor receptors, used for treating psoriasis, vascular re-occlusion, etc..
DC B02 B05
IN MAGUIRE, M P; MYERS, M R; PERSONS, P E; SPADA, A P
PA (RHON) RHONE POULENC RORER INT HOLDINGS; (RHON) RHONE POULENC RORER INT HOLDIN; (RHON) RHONE-POULENC RORER INT HOLDINGS; (RHON) RHONE POULENC RORER PHARM INC; (RHON) RHONE-POULENC RORER PHARM INC
CYC 37
PI WO 9220642 A1 921126 (9250)* EN 61 pp C07C043-21
RW: AT BE CH DE DK ES FR GB GR IT LU MC NL OA SE
W: AT AU BB BG BR CA CH CS DE DK ES FI GB HU JP KP KR LK LU MG MN MW NL NO PL RO RU SD SE US
AU 9219934 A 921230 (9313) C07C043-21
EP 584222 A1 940302 (9409) EN C07C043-21
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
JP 06507643 W 940901 (9439) C07C043-23
US 5409930 A 950425 (9522) 15 pp A61K031-495
AU 658646 B 950427 (9525) C07D213-64
EP 584222 A4 940706 (9532) C07C043-21
US 5656643 A 970812 (9738) 20 pp A61K031-47 <--
EP 584222 B1 971008 (9745) EN 44 pp C07C043-21
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69222637 E 971113 (9751) C07C043-21
ES 2108120 T3 971216 (9806) C07C043-21
ADT WO 9220642 A1 WO 92-US3736 920506; AU 9219934 A AU 92-19934 920506, WO 92-US3736 920506; EP 584222 A1 EP 92-912051 920506, WO 92-US3736 920506; JP 06507643 W WO 92-US3736 920506, JP 93-500068 920506; US 5409930 A **Cont of US 91-698420 910510**, WO 92-US3736 920506, **US 93-146072 931108**; AU 658646 B AU 92-19934 920506; EP 584222 A4 EP 92-912051 ; US 5656643 A Div ex WO 92-US3736 920506, **Div ex US 93-146072 931108, US 95-385258 950208**; EP 584222 B1 EP 92-912051 920506, WO 92-US3736 920506; DE 69222637 E DE 92-622637 920506, EP 92-912051 920506, WO 92-US3736 920506; ES 2108120 T3 EP 92-912051 920506
FDT AU 9219934 A Based on WO 9220642; EP 584222 A1 Based on WO 9220642; JP 06507643 W Based on WO 9220642; US 5409930 A Based on WO 9220642; AU 658646 B Previous Publ. AU 9219934, Based on WO 9220642; US 5656643 A Div ex US 5409930; EP 584222 B1 Based on WO 9220642; DE 69222637 E Based on EP 584222, Based on WO 9220642; ES 2108120 T3 Based on EP 584222
PRAI **US 91-698420 910510; US 93-146072 931108; US 95-385258 950208**
REP 2.Jnl.Ref ; US 4661499; WO 9116051; WO 9116305
IC ICM A61K031-47; A61K031-495; C07C043-21; C07C043-23; C07D213-64
ICS A01N043-58; A61K031-085; A61K031-40; A61K031-425; A61K031-435; A61K031-44; A61K031-50; A61K031-505; C07C043-205; C07D211-94; C07D213-30; C07D215-14; C07D215-18; C07D215-20; C07D217-16; C07D239-74; C07D239-91; C07D241-42; C07D241-52; C07D265-22; C07D277-64; C07D401-04; C07D401-06; C07D401-12; C07D407-04;

C07D409-04; C07D471-04

AB WO 9220642 A UPAB: 980309

Abnormal cell proliferation is inhibited by admin. of an epidermal growth factor (EGF) and/or platelet-derived growth factor (PDGF) receptor inhibitor (I), or its pharmaceutically acceptable salt, having a bis ring system with the first ring (hetero)aryl and the second (hetero)aryl or (hetero)carbocyclic. These rings are opt. substd. monocyclic with 0-2 heteroatoms or bicyclic with 0-4 heteroatoms.

(I) are pref. of formula (Ia), where Ar1 = opt. substd., mono- or bi-cyclic (hetero)aryl of 5-12 atoms, with N, O or S as heteroatoms (but not vicinal O and/or S); Ar2 is as Ar1 or satd. carbocyclic ring; x = (CHR1)0-4 or (CHR1)mZ(CHR1)m; Z = O, NR', S, SO or SO2; m and n = 0-3, totalling 0-3; each R = alkyl (opt. substd. by aryl, halo or carbalkoxy), alkenyl (opt. substd. by aryl or carbalkoxy), phenyl, OH, alkoxy (opt. substd. by aryl), acryloxy, halo, amino (opt. substd. by 1 or 2 alkyl), acylamino, COOH, carbalkoxy, carbaralkoxy, CONH2 (opt. substd. by 1 or 2 alkyl) or N,N-cycloalkylamido; p = 0-2; two R may together form oxo; R1 and R' = H or alkyl.

USE - (I) are useful for treating psoriasis, atherosclerosis and vascular reocclusion (esp. where this follows angioplasty). (I) inhibit the protein tyrosine kinase (PTK) portion of the EGF and PDGF receptors at concns. below those required to inhibit the PTK portion of the insulin receptor

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B04-B04D3; B04-B04J; B06-H; B07-H; B10-A10; B10-B01A; B10-B04A; B10-C02; B10-C03; B10-C04; B10-D03; B10-E02; B10-E04B; B10-G02; B10-H01; B10-H02; B12-A07; B12-F01C; B12-G01B2; B12-H03

L125 ANSWER 10 OF 10 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD

AN 92-235508 [29] WPIDS

DNC C92-106180

TI Herbicide for weed control - contg. mono carboxylic acid for synergic action with selected herbicide.

DC C03

IN CAULDER, J; CROWLEY, R H; EVANS, S L; ZORNER, P S

PA (MYCO) MYCOGEN CORP

CYC 20

PI	EP 494386	A1	920715 (9229)* EN	18 pp	A01N037-02	
	R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE					
	CA 2056290	A	920709 (9239)		A01N057-20	
	AU 9188218	A	920813 (9240)		A01N037-02	
	JP 04334303	A	921120 (9301)	12 pp	A01N037-02	
	US 5196044	A	930323 (9314)	7 pp	A01N057-12	
	AU 656744	B	950216 (9515)		A01N037-02	
	US 5681792	A	971028 (9749)	8 pp	A01N043-40	
	US 5683959	A	971104 (9750)	8 pp	A01N057-04	
	US 5683961	A	971104 (9750)	8 pp	A01N043-40	
	US 5683962	A	971104 (9750)	8 pp	A01N043-58	
	US 5703011	A	971230 (9807)	14 pp	A01N043-40	
	US 5703012	A	971230 (9807)	14 pp	A01N043-40	
	US 5703013	A	971230 (9807)	14 pp	A01N043-88	
	US 5703014	A	971230 (9807)	14 pp	A01N037-02	

ADT EP 494386 A1 EP 91-121146 920101; CA 2056290 A CA 91-2056290 911127; AU 9188218 A AU 91-88218 911127; JP 04334303 A JP 92-18401 920108; US 5196044 A US 91-638708 910108; AU 656744 B AU 91-88218 911127; US 5681792 A Div ex US 91-638708 910108, Cont of US 92-980015 921123, Cont of US 94-229866 940419, Div ex US 95-396372 950228, US 95-485334 950607; US 5683959 A Div

ex US 91-638708 910108, Cont of US 92-980015 921123, Cont of US 94-229866 940419, Div ex US 95-396372 950228, US 95-468682 950606; US 5683961 A Div ex US 91-638708 910108, Cont of US 92-980015 921123, **Cont of US 94-229886 940419**, Div ex US 95-396372 950228, US 95-466174 950606; US 5683962 A Div ex US 91-638708 910108, Cont of US 92-980015 921123, Cont of US 94-229866 940419, Div ex US 95-396372 950228, US 95-475443 950607; US 5703011 A Div ex US 91-638708 910108, Cont of US 92-980015 921123, Cont of US 94-229866 940419, Div ex US 95-396372 950228, US 95-466531 950606; US 5703012 A Div ex US 91-638708 910108, Cont of US 92-980015 921123, Cont of US 94-229866 940419, Div ex US 95-396372 950228, US 95-468677 950606; US 5703013 A Div ex US 91-638708 910108, Cont of US 92-980015 921123, Cont of US 94-229866 940419, Div ex US 95-396372 950228, US 95-468601 950607; US 5703014 A Div ex US 91-638708 910108, Cont of US 92-980015 921123, Cont of US 94-229866 940419, Div ex US 95-396372 950228, US 95-469400 950606

FDT AU 656744 B Previous Publ. AU 9188218; US 5681792 A Div ex US 5196044; US 5683959 A Div ex US 5196044; US 5683961 A Div ex US 5196044; US 5683962 A Div ex US 5196044; US 5703011 A Div ex US 5196044; US 5703012 A Div ex US 5196044; US 5703013 A Div ex US 5196044; US 5703014 A Div ex US 5196044

PRAI US 91-638708 910108; US 92-980015 921123; US 94-229866 940419; US 95-396372 950228; US 95-485334 950607; US 95-468682 950606; **US 94-229886 940419**; US 95-466174 950606; US 95-475443 950607; US 95-466531 950606; US 95-468677 950606; US 95-468601 950607; US 95-469400 950606

REP 3.Jnl.Ref ; EP 115622; JP 59193809; JP 61106501; JP 61289004; US 2622975; US 4134754; WO 8903178

IC ICM A01N037-02; A01N043-40; A01N043-58; A01N043-88; A01N057-04; A01N057-12; A01N057-20

ICS A01N031-04; A01N031-14; A01N035-10; A01N037-00; A01N037-06; A01N037-08; A01N037-10; A01N037-36; A01N039-04; A01N043-50; A01N043-76

AB EP 494386 A UPAB: 980216

Prod comprises a 7-20C monocarboxylic acid (I) or its salt and a chemical herbicide (II) for simultaneous, separate or sequential use in weed control.

Pref. the acid has 7-11C atoms, is unsubstd, satd. and is pref. decanoic or esp nonanoic acid. The herbicide is a foliar herbicide pref phenoxy acids or esters or salts; benzoic acid; aryloxyphenoxypropionate acids, esters or salts; sulphonylurea acids or esters; imidazilinones, leipyridillium, diphenyl ether acids or salts; cyclohexanedione, methane arsonate; triazine; aliphatic carboxylic acids; benzonitrile; thiocarbamate, pyrazon; glyphosate; pichloram; metribuzin; glufosinate, clopyralid; bentazon; desmedipham; quinclorac; amitrole; phenmedipham; triclopyr; or ethiozin. The herbicide is esp glyphosphate, imazethapyr, sethoxydim or paraquat. USE/ADVANTAGE - The prod. is useful as a broadrange non-selective herbicide with enhanced herbicidal effect. The ingredients are synergistic.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: C05-B01G; C10-C04E; C12-C09; C12-P05

=> d his l127-

(FILE 'USPATFULL' ENTERED AT 09:10:39 ON 04 FEB 1999)

FILE 'WPIDS' ENTERED AT 09:11:06 ON 04 FEB 1999

E GAZIT A/AU

L127 26 S E3

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                E LEVITZKI A/AU
L128          21 S E3
                E CAVENEE W/AU
L129           1 S E4
                E NAGANE M/AU
L130           1 S E3
                E HUANG H/AU
L131        4940 S HUANG ?/AU
L132           2 S L127-L131 AND APOPT?
L133           2 S L127-L131 AND TYRPHOSTIN?
L134           6 S TYRPHOSTIN?
L135           7 S L132-L134
L136           7 S L135 NOT L125

=> d all tot


L136 ANSWER 1 OF 7  WPIDS   COPYRIGHT 1999 DERWENT INFORMATION LTD
AN   98-230232 [20]   WPIDS
DNC  C98-071847
TI   Killing cancer cell by administering major histocompatibility complex or
     human lymphocytic antigen class I peptide  - useful to induce
     apoptosis in cancer cell in vivo.
DC   B04
IN   BASERGA, R L; HUANG, Z; RESNICOFF, M
PA   (UYJE-N) UNIV JEFFERSON THOMAS
CYC  20
PI   WO 9808530  A1 980305 (9820)* EN   59 pp    A61K038-00
       RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
        W: AU CA JP
     AU 9742360  A  980319 (9831)                A61K038-00
ADT  WO 9808530 A1 WO 97-US15000 970827; AU 9742360 A AU 97-42360 970827
FDT  AU 9742360 A Based on WO 9808530
PRAI US 96-704344   960828
IC   ICM  A61K038-00
AB   WO 9808530 A   UPAB: 980520
     Killing a cancer cell in a patient, comprises administering an amount of
     major histocompatibility complex (MHC) or HLA class I peptide sufficient
     to kill the cancer cell.
          Also claimed are:
          (1) a composition (A) comprising a MHC or HLA Class I peptide for use
     in the above method, and
          (2) a method for arresting growth of a cancerous tumour in a patient,
     comprising administering to the patient (A) to arrest the growth of the
     tumour, where the tumour preferably exhibits regression or is killed.
          USE - The composition can be used to induce apoptosis in a
     cancer cell in vivo (claimed).
          ADVANTAGE - The therapeutic MHC Class I peptides and compositions
     will be effective for resectable and non-resectable (i.e. metastasising)
     cancers, as well as for cancers which do not lend themselves easily to
     treatment by traditional radiation and chemotherapeutic methods, such as
     cancers of the lungs.
          Further, because cancer cells are more sensitive than normal cells to
     the toxic effects of the peptides of the invention, the methods of the
     present invention allow for aggressive treatment of cancers in patients
     without the undesirable side effects often associated with conventional
     radiation and chemotherapy treatment.
     Dwg.0/2
FS   CPI
```

FA AB; DCN
MC CPI: B04-C01B; B14-H01

L136 ANSWER 2 OF 7 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-206992 [18] WPIDS
DNC C98-065209
TI **Tyrphostin** derivatives - are useful for preventing damage to cells caused by cytotoxic and anti-neoplastic drugs and immune mediated or inflammatory response.
DC B05
IN **GAZIT, A; LEVITZKI, A;** NOVOGRODSKY, A
PA (MORR-N) MOR RES APPL LTD; (YISS) YISSUM RES & DEV CO
CYC 78
PI WO 9806391 A1 980219 (9818)* EN 92 pp A61K031-275
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9737822 A 980306 (9830) A61K031-275
ADT WO 9806391 A1 WO 97-IL276 970814; AU 9737822 A AU 97-37822 970814
FDT AU 9737822 A Based on WO 9806391
PRAI IL 96-119069 960814
IC ICM A61K031-275
ICS A61K031-415; A61K031-425; A61K031-44
AB WO 9806391 A UPAB: 980507
Compositions for countering damage to cells and tissue are new: The compositions comprise **tyrphostin** derivatives of formula (I). (I) Ar = (i) or (ii); n = 0 or when Ar = (i) then n = 0 or 1; R = CN, C(S)NH2 or C(O)NHR3, or when R1 = 4-NO2 and R2 = H or 3-OH then R may also be, , or; R3 = H, phenyl, phenyl(lower alkyl) or pyridylmethyl; R1, R2 = H, OH or NO2 or when R = CN then R1 and R2 may also be CH3, F or CF3 provided that both R1 and R2 are not H. Also claimed are compounds of formula (I) where R = CN, C(S)NH2 or C(O)NHR3, or when R1 = 4-NO2 and R2 = H then R may also be, , or; provided that (a) when R = CN and n = 0 then (aa) if one of R1 and R2 is H or OH then the other cannot be NO2, (ab) if one of R1 and R2 is H or F then the other cannot be H or F, and (b) when R1 = 4-NO2, R2 = H and n = 0 then R is not C(O)NH2 or C(S)NH2.
USE - The composition is useful for preventing damage to cells caused by cytotoxic and anti-neoplastic drugs (e.g. cisplatin, doxorubicin, cyclophosphamide, mitomycin-C and 5-fluorouracil) and immune mediated or inflammatory response. It is also useful for countering myelotoxocity, lymphotoxicity and undesired **apoptosis**.
Dwg.0/30
FS CPI
FA AB; GI; DCN
MC CPI: B07-D04C; B10-A15; B10-D03; B14-C03; B14-G02D; B14-H01

L136 ANSWER 3 OF 7 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-100721 [09] WPIDS
CR 97-011913 [01]; 97-226007 [20]
DNC C98-033220
TI Solid phase libraries containing **tyrphostin** analogues - may be used for identification of compounds useful as protein tyrosine kinase inhibitors.
DC B04 B05 D16
IN NOVA, M P; PARANDOOSH, Z; SHI, S; XIAO, X
PA (IROR-N) IRORI

CYC 78
PI WO 9749653 A2 971231 (9809)* EN 311 pp C07B061-00
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9735779 A 980114 (9822) C07B061-00
ADT WO 9749653 A2 WO 97-US11035 970624; AU 9735779 A AU 97-35779 970624
FDT AU 9735779 A Based on WO 9749653
PRAI US 96-723423 960930; US 96-20706 960624; US 96-711426 960905; US 96-709435 960906
IC ICM C07B061-00
ICS B01J019-00; B01L003-14; C07C255-41; C07C255-60; C07C323-32; C07D213-40; C07D307-52; C07D317-58; C07D333-20; C12Q001-48; G06K019-06
AB WO 9749653 A UPAB: 980302
The following are claimed: (A) a composition of compounds, comprising analogues of **tyrphostin** AG490 (which has the structure (A):

(B) a compound of formula (I) or a composition comprising at least two compounds of formula (I):

n = 0, 1, 2 or 3;

R1 = alkyl (which is straight, branched or cyclic (in which case it contains 1 ring or 2 fused rings) and preferably contains 1-15 chain C atoms), or aryl or heteroaryl (both containing 1 ring or 2 fused rings and 5-7 ring members); R1 is optionally substituted by alkyl, CN, halo, alkoxy, alkoxyalkyl, thioxy, alkylthioxy, haloalkyl, OH or amino);

R2 = alkyl (which is straight, branched and/or cyclic (in which case it contains 1 ring or 2 fused rings) and contains 1-15 chain C atoms), or aryl or heteroaryl (both containing 1 ring or 2 fused rings and 5-7 ring members); R2 is optionally substituted by one or more (R4)p;

p = 0, 1, 2 or 3;

R3 = H, Me(CH2)qC(O), or (hetero)aryl(CH2)qC(O) (optionally ring substituted by one or more R4 and containing 1 ring or 2 fused rings with 5-7 members per ring);

each R4 = alkyl, CN, halo, alkoxy, alkoxyalkyl, alkyl, thioxy, alkylthioxy, haloalkyl, OH, amino, phenoxy, alkylenedioxy, alkylenethioxyoxy or alkylenedithioxy;

In (B) when R3 is H then R1 and R2 are not (i) and (ii), or (iii) or (iv), respectively.

(C) screening for compounds which modulate the activity of protein tyrosine kinases (PTKs), comprising: (a) adding biotinylated PTK substrate to a microplate containing embedded scintillant and coated with streptavidin; (b) adding radiolabelled ATP, a test compound and PTK, under conditions such that labelled phosphate is transferred from the ATP to the bound substrate; and (c) identifying test compounds that change PTK activity; and

(D) a library comprising N compounds (N refers to undefined library), prepared by a process comprising: (a) providing N memory with matrix (MWM) combinations that have been treated to render them suitable for linking molecules; (b) selecting building blocks designated BB1, BB2 and BB2, where: (i) each member of BB1 has the formula R1CHO and the number of members of BB1 is W; (ii) each member of BB2 has the formula OHC-R2-(OH)n and the number of members of BB2 is X; (iii) each member of BB3 has the formula R3X and the number of members of BB3 is Z; and (iv) W x X x Z is N; (c) dividing the MWM combinations into W groups of N/W members and reacting each with one of the W BB1 members, so that R1 is linked to the MWM; (d) before, during or after step (c), encoding the memory with

information that identifies the BB1 group added to each MWM combination; (e) pooling the resulting MWM combinations and cyanomethylating the resulting product; (f) splitting the MWM combination into X groups of N/X members and reacting each with one of the X BB2 members via an aldol condensation; (g) before, during or after step (f) encoding the memory with information that identifies the BB2 group added to each MWM combination; (h) pooling the resulting MWM combinations, splitting them into Z groups of N/Z members and, except in instances in which BB3 is nothing, reacting each with one or the Z BB3 members; and (i) before, during or after step (h) encoding the memory with information that identifies the BB3 group added to each MWM combination.

USE - The **tyrphostin** analogues described above may be useful as tyrosine kinase inhibitors. They may thus be used as antineoplastic and antiproliferative agents, e.g. for the treatment of cancers, psoriasis, post-surgical vascular stenosis or restenosis.

ADVANTAGE- The MWMs are remotely addressable or remotely programmable recording devices, or are associated with imprinted symbology (i.e. a bar code). The memories include electronic and optical storage media. Molecules and biological particles, such as the **tyrphostin** compounds, that are in proximity or in physical contact with the matrix combination, can be labelled by programming the memory with identifying information, and can be identified by retrieving the stored information.

Dwg.0/44

FS CPI
FA AB
MC CPI: B10-B02J; B14-F01E; B14-H01; B14-H01B; B14-L06; B14-N17C; D05-H09

L136 ANSWER 4 OF 7 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-225835 [20] WPIDS
DNC C97-072304
TI Treatment of osteoarthritis by admin. of protein tyrosine kinase inhibitor - e.g. **tyrphostin** AG556 or AG82, 4,5-di anilino-phthalimide, Genistein or Herbimycin A, to slow or prevent cartilage degradation.
DC B02 B05 C02 C03
IN CAMPBELL, R N; SHARPE, T R; VASIOS, G W
PA (OSTE-N) OSTEOARTHRITIS SCI INC
CYC 75
PI WO 9711692 A2 970403 (9720)* EN 39 pp A61K031-165
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
AU 9671074 A 970417 (9732) A61K031-165
WO 9711692 A3 970703 (9743) A61K031-165
EP 850055 A2 980701 (9830) EN A61K031-165
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9711692 A2 WO 96-US14491 960911; AU 9671074 A AU 96-71074 960911; WO 9711692 A3 WO 96-US14491 960911; EP 850055 A2 EP 96-932194 960911, WO 96-US14491 960911
FDT AU 9671074 A Based on WO 9711692; EP 850055 A2 Based on WO 9711692
PRAI US 95-526290 950911
REP No-SR.Pub ; 7.Jnl.Ref ; EP 633022; WO 9200999; WO 9502420; WO 9514464
IC ICM A61K031-165
ICS A61K031-275; A61K031-365; A61K031-40; A61K031-47; A61K031-505
AB WO 9711692 A UPAB: 970828
Treatment of osteoarthritis comprises admin. of a protein tyrosine kinase inhibitor (I).

The PTK inhibitor is pref. of formula Ar-HC=C(R')(R2) (II). Ar =

3-(R1)-phenyl substd. by (OH)m; m = 1 or 2; R1 = H, OH or OMe; R2 = H or CN; R' = H, NO2, halo or organic gp. It is pref. **tyrphostin** AG556 or AG82. It may also be 4,5-dianilinophthalimide or genistein or herbimycin A.

USE - (I) inhibits interleukin-1(IL1) stimulated cartilage degradation or IL-1 stimulated biosynthesis of matrix metalloproteinase enzymes in chondrocytes in cell culture, as well as IL-1 stimulated cartilage degradation in a cartilage explant assay. Admin. is pref. oral, parenteral e.g. intra-articular (by injection) into a joint with cartilage degradation caused by osteoarthritis and in a daily dosage of 0.1-1000 (pref. 1-30) mg.

ADVANTAGE - The treatment slows or arrests the progression of the disease, unlike prior art treatments which merely alleviate its symptoms. Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: B06-H; B10-A15; B10-E04B; B14-D06; B14-N01; B06-H; C06-H; B10-A15; C10-A15; B10-E04B; C10-E04B; B14-D06; C14-D06; B14-N01; C14-N01; C06-H; C10-A15; C10-E04B; C14-D06; C14-N01

L136 ANSWER 5 OF 7 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-065155 [06] WPIDS
DNC C97-021389
TI New ((hetero)aryl)sulphonyl-phenyl-acrylonitrile cpds. - are **tyrphostin**-like tyrosine kinase inhibitors that treat cell differentiation and proliferation, esp. cancers.
DC B03 B05
IN MCMAHON, G; NEMATALLA, A S; SUN, L; TANG, P C
PA (SUGE-N) SUGEN INC
CYC 70
PI WO 9640629 A1 961219 (9706)* EN 113 pp C07C317-46
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN
AU 9661128 A 961230 (9716) C07C317-46
ADT WO 9640629 A1 WO 96-US10213 960604; AU 9661128 A AU 96-61128 960604
FDT AU 9661128 A Based on WO 9640629
PRAI US 95-480275 950607
REP 3.Jnl.Ref ; GB 1091715; GB 1191306; GB 1388867; GB 1510545; JP 61218558; WO 9426260; WO 9519169; WO 9521613; WO 9524190
IC ICM C07C317-46
ICS A61K031-10; A61K031-18; C07C311-27; C07D213-71; C07D333-34
AB WO 9640629 A UPAB: 970205
Tyrphostin-like cpds. of formula ArCH=C(CN)SO2(X)m(CH2)nQ (I) and their salts are new. Ar = phenyl (opt. substd. by 1-4 R); X = NH, C(CN)=C or CH2(CN); m = 0-1; n = 0-3; q = 1-4; Q = aryl or 5-6 membered heteroaryl opt. substd. by R; R = halo, trihalomethyl, alkyl, alkoxy, OH, NO2, CN, amido, sulphonyl, sulphonamido, COOH, carboxamide or NH2.

USE - (I) are used to treat or prevent cell proliferative disorders or cell differentiation disorders (claimed) (I) inhibit tyrosine kinase activity and are used to treat cancer, blood vessel proliferative disorders, psoriasis, hyperimmune response, and fibrotic disorders; including the cancers driven by HER-2, EGF, IGFR, PDGFR, met, SVC and KDR/FLK-1. (I) are used to treat atherosclerosis, restenosis, retinopathy, hepatic cirrhosis, glioma, head, neck, gastric, lung, breast, ovarian, colon and prostate cancer, psoriasis, diabetes mellitus, glioblastoma, melanoma, Kaposi's sarcoma, ovarian, lung mammary, prostate, pancreatic,

colon and epidermal carcinoma. They are also useful for diagnosis.
Dosage may be oral, parenteral, or transmucosal.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B07-H; B10-A08; B10-A10; B12-K04; B14-F07; B14-H01; B14-H01A; B14-H01B; B14-N12; B14-N17C; B14-S04

L136 ANSWER 6 OF 7 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 95-240368 [31] WPIDS
DNC C95-110158
TI Compsn. comprises carrier or diluent and SSI **tyrphostin** - used to treat inflammatory disorders, e.g. septic shock, rheumatoid arthritis, psoriasis, etc..
DC B05
IN **GAZIT, A; LEVITZKI, A;** NOVOGRODSKY, A
PA (KUPO-N) KUPOT HOLIM HEALTH INSURANCE INST; (YISS) YISSUM RES & DEV CO; (LEVI-I) LEVITZKI A; (KUPO-N) KUPOT-HOLIM HEALTH INSURANCE INST GEN
CYC 58
PI WO 9514464 A1 950601 (9531)* EN 49 pp A61K031-165
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK ES FI GB GE HU JP KE KG KP KR KZ LK LT LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA US UZ VN
AU 9512935 A 950613 (9539) A61K031-165
EP 731697 A1 960918 (9642) EN A61K031-165
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 10504014 W 980414 (9825) 40 pp C07C255-40
ADT WO 9514464 A1 WO 94-US13535 941123; AU 9512935 A AU 95-12935 941123; EP 731697 A1 WO 94-US13535 941123, EP 95-904123 941123; JP 10504014 W WO 94-US13535 941123, JP 95-515214 941123
FDT AU 9512935 A Based on WO 9514464; EP 731697 A1 Based on WO 9514464; JP 10504014 W Based on WO 9514464
PRAI IL 93-107736 931124
REP 04Jnl.Ref ; EP 322738; EP 444899; EP 537742; JP 62039558; US 5217999; WO 9116892; WO 9426260
IC ICM A61K031-165; C07C255-40
ICS A61K031-275; C07C255-41
AB WO 9514464 A UPAB: 950810
Pharmaceutical compsn. comprises (a) physiologically acceptable carrier or diluent; and (b) a therapeutically effective amt. of a SSI **tyrphostin**, Also claimed are methods of treating inflammatory disorders, preventing LPS induced toxicity, reducing LPS induced increase in TNF-alpha levels, preventing TNF-alpha induced toxicity and inhibiting NO2 production comprising administering SSI **tyrphostin**. Also claimed are SSI **tyrphostin** cpds. selected from SSI 19, SSI 20, SSI 21, SSI 22, SSI 23 and SSI 24.
USE - The compsn. is useful to treat inflammatory disorders e.g. septic shock, rheumatoid arthritis, psoriasis, HIV-1, chronic granulomutotic diseases, tuberculosis, leprosy, neurological inflammatory conditions, multiple sclerosis, graft versus host diseases and atherosclerosis. The compsn. may also be used to treat sepsis, psoriasis or AIDS related cachexia.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B10-A15; B10-B02J; B10-D01; B14-A01B1; B14-A02B1; B14-C03; B14-C09B; B14-F07; B14-G02C; B14-N17C; B14-S01; B14-S06

L136 ANSWER 7 OF 7 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 91-341728 [47] WPIDS
CR 93-213795 [26]; 95-088809 [12]; 96-353855 [35]
DNC C91-147441
TI Use of kinase and phosphatase modulators of protein phosphorylation - for treatment and diagnosis of amyloidosis associated with Alzheimer's disease.
DC B05
IN BUXBAUM, J D; GANDY, S E; GREENGARD, P
PA (UYRQ) UNIV ROCKEFELLER; (BUXB-I) BUXBAUM J D
CYC 16
PI EP 457295 A 911121 (9147)*
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
CA 2042668 A 911117 (9207)
EP 457295 A3 920805 (9336)
JP 07025786 A 950127 (9514) 11 pp A61K045-00
EP 457295 B1 970409 (9719) EN 18 pp A61K031-00
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69125523 E 970515 (9725) A61K031-00
ES 2102986 T3 970816 (9740) A61K031-00
ADT EP 457295 A EP 91-107844 910515; EP 457295 A3 EP 91-107844 910515; JP 07025786 A JP 91-136925 910514; EP 457295 B1 EP 91-107844 910515; DE 69125523 E DE 91-625523 910515, EP 91-107844 910515; ES 2102986 T3 EP 91-107844 910515
FDT DE 69125523 E Based on EP 457295; ES 2102986 T3 Based on EP 457295
PRAI US 90-524202 900516
REP NoSR.Pub ; 6.Jnl.Ref ; EP 215171
IC A61K031-00; A61K037-02; C12Q001-42
ICM A61K031-00; A61K045-00
ICS A61K037-02; C12Q001-42
ICA C12N009-99
AB EP 457295 A UPAB: 971030
The use of kinase or phosphatase modulators (I) in regulating protein phosphorylation is claimed. (I) are capable of increasing or decreasing the rate of proteolytic processing of proteins found in intracellular neurofibrillary tangles and extracellular amyloid plaques.

(I) is either a kinase stimulator selected from phorbol ester, indolactam, mezerin, diacrylglycerol or forskolin, or a kinase inhibitor selected from staurosporine, auranofin, W5, W12, W13, W7, H7, H8, H9, HA1004, sphingosine or **tyrphostin**. (I) may also be a phosphatase stimulator, preferably a somatostatinm analogue, or a phosphatase inhibitor, such as okadaic acid derivatives calyculin-A or vanadate. The proteins are selected from betaA4 precursor protein, tau or a neurofilament protein. Also claimed is an in vitro method of screening for an agent that modulates amyloid formation comprising contacting mammalian cells with an agent suspected of being capable of modulating protein phosphorylation and detecting any alterations in the degradation of the amyloid precursor protein.

USE/ADVANTAGE - (I) are used in the treatment of amyloidosis associated with Alzheimer's disease (claimed). Administration can be oral, parenteral, perlingual, rectal or local in a dose of 0.05-20 mg/kg. (I) can also be used for diagnostic screening of an agent which modulates amyloid formation, by administering (I) to a normal or transgenic mammal and detecting neurodegenerative changes in the brain (claimed). @(15pp Dwg.No 0/5)
FS CPI
FA AB; DCN
MC CPI: B04-B02C3; B04-B04F; B09-C02; B12-G01; B12-G04A; B12-K04E

```
=> dhis l137-

DHIS IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d his l137-


     (FILE 'WPIDS' ENTERED AT 09:11:06 ON 04 FEB 1999)
L137        1444 S TYROSINE(L)KINASE OR PROTEIN(L)KINASE OR ?TYROSINEKINAS? OR ?
L138          35 S L137 AND APOPTOS?
L139           2 S L138 AND (DELTAEGF# OR EGF# OR EPIDERM? (L) GROWTH?)
L140           2 S L139 NOT L125,L136
L141          33 S L138 NOT L125,L136,L140
L142          21 SEA L141 AND P63?/M0,M1,M2,M3,M4,M5,M6
L143          25 S L141 AND (?NEOPLAS? OR ?CANCER?)
L144          28 S L142,L143
L145           5 S L141 NOT L144

=> d all l140 tot


L140 ANSWER 1 OF 2  WPIDS   COPYRIGHT 1999 DERWENT INFORMATION LTD
AN   98-120021 [11]   WPIDS
DNC  C98-039435
TI   Use of sphingosine-1-phosphate  - to retard apoptosis in
     degenerative diseases e.g. neuro-degenerative disease, ischaemic stroke
     and aging.
DC   B05 D21 E16
IN   SPIEGEL, S
PA   (SPIE-I) SPIEGEL S
CYC  1
PI   US 5712262  A  980127 (9811)*       4 pp    A61K031-66
ADT  US 5712262 A US 96-754323 961121
PRAI US 96-754323   961121
IC   ICM  A61K031-66
AB   US 5712262 A   UPAB: 980316
     Use of sphingosine-1-phosphate (I) to delay programmed cell death is new.
          USE - (I) induces mitogenesis, is a second messenger in cellular
     proliferation induced by platelet-derived growth factor and
     serum and counteracts the action of programmed cell death. (I) retards
     apoptosis in degenerative diseases such as neurodegenerative
     disease, ischaemic stroke and aging (especially in epidermal
     tissue) and slows the degenerative process in patients suffering from
     these diseases. (I) prevents the appearance of the features of
     apoptosis, i.e. intranucleosomal DNA fragmentation and
     morphological changes which are caused by increased concentrations of
     ceramide. Inhibition of ceramide mediated apoptosis by
     activation of protein kinase C is due to stimulation
     of sphingosine kinase and an increase in (I). (I) stimulates the
     extracellular signal regulated kinase pathway and counteracts
     the ceramide induced activation of stress activated protein
     kinase.
     Dwg.0/0
FS   CPI
FA   AB; DCN
MC   CPI: B05-B01G; B14-J01; B14-R01; D08-B09A; E05-G09D
```

L140 ANSWER 2 OF 2 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-424764 [39] WPIDS
DNC C97-135900
TI Composition comprising **tyrosine kinase** inhibitor linked to **epidermal growth** factor - induces **apoptosis** and clonogenic cell death in, e.g. breast and prostate cancer.
DC B02 B04
IN UCKUN, F M
PA (MINU) UNIV MINNESOTA
CYC 74
PI WO 9729779 A2 970821 (9739)* EN 66 pp A61K047-48
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN YU
AU 9719588 A 970902 (9751) A61K047-48
WO 9729779 A3 971030 (9815) A61K047-48
ADT WO 9729779 A2 WO 97-US2325 970214; AU 9719588 A AU 97-19588 970214; WO 9729779 A3 WO 97-US2325 970214
FDT AU 9719588 A Based on WO 9729779
PRAI US 96-602186 960216
REP 1.Jnl.Ref ; WO 8800837; WO 9320834; WO 9501806; WO 9606116
IC ICM A61K047-48
AB WO 9729779 A UPAB: 970926
Composition comprises a **tyrosine kinase** inhibitor (TKI) linked to **epidermal growth** factor (**EGF**), where the composition binds to **EGF** receptors present on the surface of a cell, and inhibits **tyrosine kinases** associated with the **EGF** receptor, thereby inducing **apoptosis** and clonogenic cell death.

Also claimed are:

(1) a composition comprising genistein covalently linked to **EGF**, and

(2) a method for killing cancer cells in vivo without causing significant toxicity, which comprises administering the composition as above to cancer cells expressing **EGF** receptors.

USE - The composition can be for the treatment of breast cancer and prostate cancer (claimed). It can also be used for the treatment of lung cancer, head and neck cancer, bladder cancer, cancer of the stomach, cervix and ovary melanoma and brain tumours. Conjugates of **EGF**-genistein were found to bind with high affinity to the **EGF** receptor on breast cancer cells and trigger their rapid apoptotic cell death, killing > 99.99% of clonogenic breast cancer cells in vitro.

Also, **EGF**-genistein was shown to be very well tolerated by SCID mice, as well as monkeys and showed potent antitumour activity against cancer xenografts.

The composition can be administered orally and parenterally, as well as by intra-venous, intra-muscular or subcutaneous routes at a dosage as low as 25 mg/kg.

ADVANTAGE - **EGF**-genistein markedly improves the long-term tumour-free survivor of immunodeficient SCID mice xenografted with metastatic human breast cancer and it was superior to methotrecate, adriamycin and cyclophosphamide. It also does not cause liver toxicity in mice, even though a substantial proportion of the composition moves to the liver. Therefore, even though **EGF**-RC is expressed not only on cancer cells but on many normal tissues as well, **EGF**-genistein

is a cancer specific drug which kills cancer cells by inactivation of life-maintaining enzyme complexes which are unique to them.
Dwg.0/15
FS CPI
FA AB; DCN
MC CPI: B04-H06A; B06-A01; B14-H01; B14-N08

=> d l144 bib abs tot

L144 ANSWER 1 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-594494 [50] WPIDS
DNN N98-462618 DNC C98-178289
TI Evaluating function of receptor **protein tyrosine kinase** in ligand-independent assay - using cells expressing chimaeric receptors, the extracellular domain of which is recognised by specific antibody, used to identify **kinase** modulators, particularly for treating neurodegenerative diseases.
DC B04 D16 J04 S03
IN CLARY, D
PA (SUGE-N) SUGEN INC
CYC 82
PI WO 9845708 A1 981015 (9850)* EN 80 pp
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
ADT WO 9845708 A1 WO 98-US6842 980407
PRAI US 97-51715 970703; US 97-43207 970408
AN 98-594494 [50] WPIDS
AB WO 9845708 A UPAB: 990107
A function of a receptor **protein tyrosine kinase** (A) is evaluated by (a) transfecting cells with a vector encoding a chimaera of (i) an extracellular region (ECR) with (ii) the intracellular region of (A); (b) treating the cells with an antibody (Ab) specific for ECR and (c) monitoring any effects on the cells.Also new are (1) identification of compounds (I) that modulate function of (A) in cells using a similar method but with the cells additionally treated with test compound; (2) identification of compounds (Ia) that modulate the C-RET (A) by monitoring the effect of test compounds on C-RET expressing cells; (3) preventing or treating conditions, in mammals, caused by aberrant cell survival by administering a modulator of (A).

USE - Method (3) is especially applied to neurodegenerative conditions involving C-RET, specifically Alzheimer's or Parkinson's diseases or amyotrophic lateral sclerosis, based on the observation that C-RET activation is essential for neuron survival. Other conditions involving cell proliferation and differentiation may also be treated, e.g. **cancer**, angiogenesis, wound healing, psoriasis, diabetes mellitus, restenosis, inflammation or abnormal **apoptosis**.

ADVANTAGE - The method can be used even when the native ligand for (A) is unknown, and avoids use of ligands that may activate several receptors. It is thus specific and versatile (almost any (A) can be the source of ICR), and use of different species to provide ECR and ICR ensures that Ab reacts only with the chimaeric receptor.
Dwg.0/0

L144 ANSWER 2 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD

AN 98-542695 [46] WPIDS
DNC C98-163133
TI New method of modulating the activity of nm23 in individuals at risk from proliferative disorders - by modulating the level of Rad activity.
DC B04 D16
IN KAHN, C R; ZHU, J
PA (JOSL-N) JOSLIN DIABETES CENT INC
CYC 81
PI WO 9844088 A2 981008 (9846)* EN 32 pp
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
ADT WO 9844088 A2 WO 98-US6521 980402
PRAI US 97-43983 970403
AN 98-542695 [46] WPIDS
AB WO 9844088 A UPAB: 981118
New method of modulating the activity of nm23 in a subject at risk from a proliferative disorder, comprising modulating the level of Rad activity.

USE - The method can be used to modulate insulin-related disorders (type II diabetes, obesity, disorders involving insulin-stimulated glucose transport, or disorders characterized by abnormally high/low levels of Rad activity/expression), cell development (e.g. Neural or muscle cell), preferably cultured cells with the aim of promoting wound healing or tissue replacement, cell **apoptosis** (e.g. **Cancer**, including those with metastatic potential, melanoma, breast/hepatocellular carcinoma, leukemia, colon/colorectal carcinomas, and ovarian carcinomas), disorders characterized by unwanted cell proliferation/cell migration, cell mobility/motility, and Rad activity in a cell/subject. The method can also evaluate the metastatic potential of a cell (e.g. A tumour from a subject), and determine whether a subject mammal (e.g. Human or primate) is at risk from disorders related to unwanted cell proliferation, insulin-related disorders, and metastasis. The method may evaluate the ability of b oth Rad and nm23 **protein** fragments/analogues to interact with each other both in vitro and in vivo, and is particularly useful for identifying fragments/analogues of both **proteins**, which have biological activity or can bind each other. The method can evaluate a test compound (e.g. Inhibitor) to modulate an interaction between a Rad and nm23 polypeptide. The same can be achieved through a two-phase method. The method can be performed in a cell-free system (e.g. A cell lysate or reconstituted **protein** mixture). A two-phased method can be used to evaluate a treatment and (as a single phase) it's ability to modulate a Rad-nm23 interaction. The method may also be performed on rodents.

ADVANTAGE - The method offers a novel bimolecular, bidirectional mechanism of regulating Rad-nm23 interaction. This is achieved by nm23 modulating Rad activity through altering the balance of GTP and GTP loading, while Rad regulates nm23 activity as an NDP **kinase**.
Dwg.0/0

L144 ANSWER 3 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-531699 [45] WPIDS
DNC C98-159508
TI Inhibiting growth or inducing **apoptosis** in tumour cells - by contact with chelerythrine and ionising radiation, effective against radio-resistant tumours.
DC B02

IN CHMURA, S J; KUFE, D W; QUINTANS, J; WEICHSELBAUM, R R
PA (ARCH-N) ARCH DEV CORP; (DAND) DANA FARBER CANCER INST INC
CYC 81
PI WO 9842339 A1 981001 (9845)* EN 73 pp
RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
ADT WO 9842339 A1 WO 98-US5842 980325
PRAI US 97-826814 970325
AN 98-531699 [45] WPIDS
AB WO 9842339 A UPAB: 981111
A method for inhibiting growth of tumour cells, inducing **apoptosis** in tumour cells, killing tumour cells or treating **cancer** comprises contacting the tumour cells with chelerythrine of formula (I) and with ionising radiation. The dose of (I), when combined with the dose of ionising radiation, is effective to inhibit growth, induce **apoptosis**, kill the tumour cells or treat the **cancer**.
Also claimed is a method of potentiating the effect of ionising radiation on tumour cells comprising contacting the cells with (I) and then contacting with ionising radiation.
USE - Tumours which can be treated include tumours of the brain (glioblastomas, medulloblastoma, astrocytoma, oligodendroglioma and ependymomas), lung, liver, spleen, kidney, lymph node, small intestine, pancreas, blood cells, colon, stomach, breast, endometrium, prostate, testicle, ovary, skin, head and neck, oesophagus, bone marrow, blood (leukaemia), cervix or other tissue.
ADVANTAGE - A combination of a low dose of (I) (a known **protein kinase** C inhibitor) and a low dose of ionising radiation is effective in killing radio-resistant tumour cells, since (I) overcomes the resistance to **apoptosis** of radio-resistant cells.
Dwg.0/17

L144 ANSWER 4 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-531534 [45] WPIDS
DNN N98-414794 DNC C98-159402
TI Control of, e.g. growth, detachment and **apoptosis** in cells through receptor/PTK-STAT pathway - useful for, e.g. treating **cancer**, autoimmune disease, neurodegeneration and diagnosis based on STAT levels and clones overexpressing STAT.
DC B04 D16 S03
IN CHIN, Y E; FU, X; XIE, B
PA (UYYA) UNIV YALE
CYC 21
PI WO 9841090 A1 980924 (9845)* EN 135 pp
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
ADT WO 9841090 A1 WO 98-US5307 980319
PRAI US 97-41410 970319
AN 98-531534 [45] WPIDS
AB WO 9841090 A UPAB: 981111
The rate and/or amount of a cellular process, i.e. growth, detachment, migration or **apoptosis**, is modulated by altering the Receptor/PTK (**protein tyrosine kinase**)-STAT (A) pathway in the cell. Also new are: (1) a method of identifying: (a) inhibitor of **apoptosis** (I) that blocks phosphorylation of (A) by **tyrosine kinase** (TK), and (b) promoter of

apoptosis (II) that stimulates such phosphorylation; (2) assay for STAT-mediated **apoptosis** by determining phosphorylation of (A); (3) assay for diagnostic agents (III) useful for measuring (A) activation; (4) a clone that produces higher exogenous levels of STAT than its parental cell line; (5) diagnosis of abnormal, disease-related STAT activation, and (6) detecting amount of phosphorylated STAT **protein** using anti-phosphotyrosine-STAT.

USE - Altering the (A) pathway is used to treat diseases and developmental defects caused: (a) by abnormal induction of cell death, by promoting (in cases of **cancer**, autoimmune disease, viral susceptibility or obesity) or inhibiting (e.g. in degenerative diseases such as Parkinson's or Alzheimer's, ischaemic injury, virus infection, including human immune deficiency virus, or inflammation) **apoptosis**; (b) by abnormal cell proliferation (**cancer** or metastases), by inhibiting cell growth; (c) by cell growth retardation, or (d) by abnormal cell attachment. Particularly an agent that increases (decreases) phosphorylation of (A), or the nucleic acid encoding it, is administered. In method (2), high levels of (A) **protein** are diagnostic of thanatophoric dysplasia type II, FGFR (fibroblast growth factor receptor)-associated disease, **cancer** (or metastasis), autoimmune or degenerative diseases, diabetes, aging and inflammation. Method (5) is also used to diagnose such diseases. The clones of (4) are used to identify (I); (I) and (II) are potential therapeutic agents. The methods are based on the discovery that activation of (A) causes **apoptosis** and cell growth arrest; inhibits cell proliferation and stimulates detachment and migration. Therapeutic agents are administered orally, by injection and topically, typically at 0.1-100 (especially 0.1-1) mu g/kg.

Dwg.0/30

L144 ANSWER 5 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-481194 [41] WPIDS
CR 98-481213 [41]; 98-481214 [41]
DNC C98-145699
TI New isolated component of bromelain - used for treating e.g. auto immune diseases, transplant rejection, allergic reactions, toxic shock, **apoptosis**, parasite or pathogen infections or **cancer**.
DC B04 C03 D16
IN ENGWERDA, C; MYNOTT, T L; PEEK, K
PA (CORT-N) CORTECS UK LTD
CYC 81
PI WO 9838291 A1 980903 (9841)* EN 55 pp
RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
ADT WO 9838291 A1 WO 98-GB590 980225
PRAI GB 97-6119 970325; GB 97-3827 970225; GB 97-3850 970225; GB 97-4252 970228
AN 98-481194 [41] WPIDS
CR 98-481213 [41]; 98-481214 [41]
AB WO 9838291 A UPAB: 981014
A component of bromelain (a proteolytic enzyme from the plant Bromeliaceae) which contains **proteins** having molecular weights of approx. 15.07 kD, 25.85 kD and 27.45 kD as determined by SDS-PAGE, has isoelectric points of 10.4 and 10,45 and is obtainable by:(a) dissolving bromelain in acetate buffer at pH 5.0; (b) separating the components of

the bromelain by fast flow high performance chromatography on ''S-Sepharose'' (RTM) eluting with a linear gradient of 0 to 0.8M NaCl in acetate buffer over 300ml; (c) collecting the fraction corresponding to the final double peak off the column; and (d) isolating the **protein** from the fraction collected in (c).

Also claimed is a pharmaceutical or veterinary composition comprising the CCS fraction of bromelain together with an excipient.

USE - Ananain, comosain, a mixture of ananain and comosain or a component of bromelain can be used in: (a) the preparation of an agent for modulating intracellular signalling pathways which control cell growth and proliferation; (b) the preparation of an agent for inhibiting the production of growth factors and cytokines by cells; (c) the preparation of an agent for reducing or preventing the activation of the mitogen-activated **protein** (MAP) **kinase** pathway; (d) the preparation of an agent for reducing or preventing the activation of T cells; (e) as an immunosuppressive agent; (f) the preparation of an agent for blocking the production of growth factors and other cytokines or for the treatment or prevention of autoimmune diseases, graft or transplant rejection by a host, allergic reactions, toxic shock, **apoptosis**, parasite or pathogen infections or **cancer**. The CCS fraction of bromelain can be used in the conjunction with ananain and comosainin the preparation of an agent for the treatment or prevention of diseases and conditions mediated by: (a) the activation of T cells; (b) activation of the MAP **kinase** pathway; or (c) the production of growth factors or cytokines; or in the treatment or prevention of **cancer**. (All claimed)

The products can be used for treating e.g. **cancers**, autoimmune diseases such as rheumatoid arthritis, type-1 diabetes mellitus, multiple sclerosis, Crohn's disease, lupus, graft or transplant rejection, allergies, toxic shock, **apoptosis** in e.g. HIV infection and ageing or parasite or pathogenic infection.

Dwg.0/15

L144 ANSWER 6 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-207049 [18] WPIDS
DNN N98-164444 DNC C98-065265
TI Serine-phosphorylated Bcl-X-l/Bcl-2 Associated cell Death regulator polypeptide - useful for modulation of **apoptosis** associated with, e.g. **cancer** and immunodeficiency diseases.
DC B04 D16 S03
IN KORSMEYER, S J
PA (UNIW) UNIV WASHINGTON
CYC 21
PI WO 9809643 A1 980312 (9818)* EN 62 pp
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 9744110 A 980326 (9832)
ADT WO 9809643 A1 WO 97-US15871 970909; AU 9744110 A AU 97-44110 970909
FDT AU 9744110 A Based on WO 9809643
PRAI US 96-707868 960909
AN 98-207049 [18] WPIDS
AB WO 9809643 A UPAB: 980507
New isolated and substantially purified serine-phosphorylated BAD (Bcl-Xl/Bcl-2 Associated cell Death regulator) polypeptide (A) comprises a sequence which: (a) lacks the C-terminal signal-anchor sequence characteristic of the membrane bound members of the Bcl-2 family; (b) lacks BH3 and BH4 domains; (c) has a BH1 and BH2 domain; (d) has a phosphorylated Serine 112, and (e) binds to a 14-3-3 **protein** or a fragment of the sequence. Also claimed are: (1) a method to

prevent/treat increased/decreased **apoptosis** in a cell by administration of: (i) an inhibitor/activator of phosphoserine phosphatase on (A), or (ii) a serine **kinase** inhibitor/activator which inhibits/increases phosphorylation and binding of (A) to a 14-3-3 **protein**, and (2) a method for identifying an agent which modulates phosphorylation of BAD by administering the agent to a cell line which expresses BAD and a 14-3-3 **protein** and detecting a change in the phosphorylation of BAD compared to a pretreatment value.

USE - Modulators of phosphorylated BAD, which act through inhibition/activation of a phosphoserine phosphatase, are useful for preventing/treating increased/decreased **apoptosis** in a cell. The increased **apoptosis** may result from immunodeficiency diseases, senescence, neurodegenerative disease, ischaemic cell death, reperfusion cell death, infertility and wound-healing. Decreased **apoptosis** may result from **cancer**, viral infection, lymphoproliferative conditions, arthritis, infertility, inflammation and autoimmune diseases. Measuring the amount of phosphorylated compared to unphosphorylated BAD polypeptide and/or total BAD in a cell is useful for determining the apoptotic state of a cell. (All claimed).

Dwg.0/9

L144 ANSWER 7 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-169174 [15] WPIDS
DNC C98-054278
TI New nucleic acid encoding vertebrate related adhesion focal **tyrosine kinase** - useful for, e.g. regulating growth, differentiation, adhesion and migration of cells, used for treating metastases.
DC B04 D16
IN AVRAHAM, H; AVRAHAM, S; GROOPMAN, J E
PA (BETH-N) BETH ISRAEL DEACONESS MEDICAL CENT
CYC 20
PI WO 9807870 A1 980226 (9815)* EN 167 pp
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9741479 A 980306 (9830)
ADT WO 9807870 A1 WO 97-US14093 970812; AU 9741479 A AU 97-41479 970812
FDT AU 9741479 A Based on WO 9807870
PRAI US 97-816462 970313; US 96-703623 960823
AN 98-169174 [15] WPIDS
AB WO 9807870 A UPAB: 980410

Isolated RAFTK (related adhesion focal **tyrosine kinase**) nucleic acid (I) from a vertebrate, is new. Also claimed are: (1) expression vector comprising (I) and regulators; (2) host cells transfected with the vector; (3) transgenic animals in which the gene encoding functional RAFTK polypeptide (II) is enhanced, induced, prevented or suppressed; (4) isolated, biologically active (II) from a vertebrate; (5) fusion **protein** comprising (II); (6) antibody (Ab) reactive with an epitope of (II); (7) an assay for identifying cells at risk of unwanted proliferation or differentiation by detecting: (i) aberrant modification or mutation in a gene encoding (II), or (ii) misexpression of this gene; (8) megakaryocytes or platelets produced by modulating (II) activity in progenitor stem cells; (9) an assay for screening compounds for modulation of RAFTK interaction with cellular **proteins**, and (10) RATFK inhibitors (III) identified by the assay of (9).

USE - Cells of (2) can be used to produce recombinant (II) (claimed), e.g. for use in raising Ab, useful for detecting/assaying (II) for diagnosis or prognosis in any standard immunoassay format, or for screening cDNA expression libraries. Agents that modulate (II) are used to

control growth, differentiation, haematopoiesis or survival of cells (claimed) (especially mast cells, melanocytes and megakaryocytes) or adhesion (especially focal adhesion formation), migration, phagocytosis or motility of cells, particularly for treating metastases. Typical applications of modulation of (II) are in treatment of immune-mediated diseases, e.g. **cancer** or leukaemia, where **apoptosis** is induced, inhibition of **apoptosis** where this is induced by radiation, chemotherapy or neurodegenerative disease, and also for expanding cells for transplantation, treating conditions associated with megakaryocyte abnormality, e.g. thrombocytopaenia, and control of platelet aggregation. Fragments of (I) are useful as probes and primers in the assay of (6) or for identifying related sequences, and also therapeutically as antisense, ribozyme or triplex-forming molecules. Animals of (3) are useful as models for cellular/tissue disorders associated with altered RAFTK alleles, and also for drug screening and recombinant (II) production. (I), (II), (III) may be administered by injection or inhalation, orally, or they are expressed from nucleic acid introduced in standard gene therapy vectors.
Dwg.1/5

L144 ANSWER 8 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-168878 [15] WPIDS
DNC C98-054055
TI Treating or preventing restenosis by administration of inhibitor of **protein kinase** C - also for treatment of other proliferative diseases, especially **cancer**, particularly applied topically in hydrogel.
DC A25 A96 B02 B04
IN PRESCOTT, M F
PA (NOVS) NOVARTIS AG
CYC 79
PI WO 9807415 A2 980226 (9815)* EN 28 pp
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
ZA 9707433 A 980429 (9822) 26 pp
AU 9742055 A 980306 (9830)
ADT WO 9807415 A2 WO 97-EP4503 970818; ZA 9707433 A ZA 97-7433 970819; AU 9742055 A AU 97-42055 970818
FDT AU 9742055 A Based on WO 9807415
PRAI US 96-25072 960830; US 96-24219 960820
AN 98-168878 [15] WPIDS
AB WO 9807415 A UPAB: 980410
Treatment and prevention of restenosis after re-vascularisation comprises administering an inhibitor (I) of **protein kinase** C (PKC).

More generally administration of (I) is used prevent or alleviate smooth muscle cell (SMC) proliferation.

USE - The method is particularly used after balloon angioplasty of, e.g. a coronary artery. Not only is proliferation of SMC prevented, but also **apoptosis** is stimulated, matrix deposition inhibited and late lesions (those developing 3-9 months after injury) are prevented.

Preventing these lesions requires inhibition of intimal SMC proliferation, not just SMC migration.Also (not claimed) treatment with (I) is used generally to treat diseases involving cellular proliferation and/or decreased **apoptosis**, specifically **cancer**,

especially when administered locally.

(I) are administered locally, preferably in a hydrogel, specifically an oxyalkylene or a polyoxyalkylene polymer, or systemically.

For treating restenosis, the usual dose in 200-10000 (preferably 500-1000) mu g per site (typically 10-100 mm2), and for treatment of **cancers** at 200-10000 (preferably 500-1000) mu g/day.

When (I) is an antisense molecule it is administered to provide 50-1000 (preferably at least 200) nM.

ADVANTAGE - The preferred (I), N-benzoyl-staurosporine (Ia; US5093330) inhibits several isoforms of PKC involved in phosphorylation of **proteins** critical for cellular proliferation and differentiation, including platelet-derived and fibroblast growth factor **tyrosine kinases**.

Localised delivery of (I) ensures high concentration at the target site and minimises systemic concentrations and thus potential toxicity on other proliferating tissues.

Dwg.0/0

L144 ANSWER 9 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-167929 [15] WPIDS
CR 96-259065 [26]; 97-153579 [14]; 98-051490 [05]
DNC C98-053733
TI DNA encoding human p21-activated **kinase** p65 **protein** - useful in screening drugs for potential use in the treatment of **cancer**, arthritis, autoimmuine disease, inflammation, **apoptosis** related disorders, etc..
DC B04 D16
IN ABO, A; MARTIN, G A
PA (ONYX-N) ONYX PHARM INC
CYC 1
PI US 5698445 A 971216 (9815)* 42 pp
ADT US 5698445 A Cont of US 95-369780 950106, US 96-636036 960422
FDT US 5698445 A Cont of US 5518911
PRAI US 95-369780 950106; US 96-636036 960422
AN 98-167929 [15] WPIDS
CR 96-259065 [26]; 97-153579 [14]; 98-051490 [05]
AB US 5698445 A UPAB: 980410

An isolated nucleic acid comprising a sequence having at least 95% identity to one of the following sequences is new: (a) nucleotides (nt) 391-1908 of (I); (b) nt 535-729 of (I); (c) nt 1081-1848 of (I); (d) nt 391-1833 of (I); or (e) nt 391-1854 immediately followed by nt 1864-1980 of (I).

(I) is a 2248 bp cDNA sequence encoding a 506 amino acid new human serine **protein kinase** designated human p21-**protein** activated serine **kinase** p65 **protein** (hPAK65)

Also claimed are: (1) a vector containing a nucleic acid as above; and (2) a host cells transformed with a nucleic acid as above.

USE - hPAK65 nucleic acids and polypeptides can be used to modulate human rac1- and CDC42Hs-related pathways, to identify hPAK65-related pathways and diseases, and to identify agents that modulate hPAK65 activity. Such agents can be used to treat **cancer**, arthritis, angiogenesis, inflammation, autoimmune diseases, **apoptosis**, etc.

Dwg.0/10

L144 ANSWER 10 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-130704 [12] WPIDS
DNN N98-103099 DNC C98-043258
TI New RNA dependent **protein kinase** peptide antagonist(s)

- used for stimulating cell proliferation under conditions of cell cycle arrest, quiescence, reduced growth or cell death.

DC B04 D16 S03
IN BOTTARO, D P; PETRYSHYN, R
PA (USSH) US SEC DEPT HEALTH; (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 77
PI WO 9804717 A2 980205 (9812)* EN 61 pp
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU
AU 9739824 A 980220 (9828)
ADT WO 9804717 A2 WO 97-US14350 970729; AU 9739824 A AU 97-39824 970729
FDT AU 9739824 A Based on WO 9804717
PRAI US 96-23307 960730
AN 98-130704 [12] WPIDS
AB WO 9804717 A UPAB: 980323

An isolated double-stranded (ds) RNA dependent **protein kinase** (b) peptide antagonist (A) of less than 50 amino acid residues in length is claimed comprising at least 8 contiguous amino acid residues from a sequence selected from (I)-(VI) given below in one letter amino acid code, or a conservatively modified variant, where the variant forms a complex with regulatory RNA.

AKGRSKQEAR (I)
GEGRSKKEAK (II)
GSGSTKQEAK (III)
GSGVTKQEAK (IV)
GSGTSKKLAK (V)
GTGSTKQEAK (VI)

Also claimed are: (1) a nucleic acid (I) encoding (A); (2) an expression vector comprising (I); (3) a kit to rapidly determine the presence in a biological sample of PKR which is unable to form a complex with regulatory RNA, comprising: (a) a stable preparation of (I); (b) a hybridisation solution in either dry or liquid form for the hybridisation of probes to target PKR nucleic acids; (c) a solution for washing and removing undesirable and non-hybridised nucleic acids; (d) a substrate for detecting the hybridisation complex; and (e) instructions for performing and interpreting the assay; (4) an antibody specifically reactive with a PKR peptide antagonist, where the peptide antagonist comprise a recombinant or synthetic peptide comprises at least seven amino acids of (I) to (VI); and (5) a host cell comprising an expression vector as in (2).

USE - The PKR antagonists can inhibit activation of ds RNA dependent PKR to stimulate cell proliferation under conditions of cell cycle arrest, quiescence, reduced growth or cell death. They can be used for treating conditions in which cell proliferation is desirable, such as triggering self-replication and expansion of haematopoietic and other stem cells, stimulating bone replacement following fracture, osteoporosis or arthritis, promoting regeneration of cells otherwise difficult to proliferate (e.g. muscle, nerve), treating sickle cell disease by stimulating foetal-haemoglobin producing cells, reducing cell death by reducing cell lysis caused by viral infection, reducing cell death by inhibiting **apoptosis** mediated by PKR, restoring T cell populations in immune compromised patients, and inhibiting TAR RNA activation of PKR in HIV-1 infected individuals. They can also be used for stimulating wound healing or for ex vivo proliferation of dermal fibroblasts and/or immature keratinocytes for use in skin grafts. The products can also be used for detection.

Dwg.0/0

L144 ANSWER 11 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-086658 [08] WPIDS
DNC C98-029287
TI Enhancement of **cancer** cell **apoptosis** - by introducing nucleic acid encoding human double-stranded RNA dependent **protein kinase** into **cancer** cells, useful in, e.g. treating cervical **cancer**.
DC B04 D16
IN LAU, A; YEUNG, M
PA (REGC) UNIV CALIFORNIA
CYC 78
PI WO 9800013 A1 980108 (9808)* EN 67 pp
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9735837 A 980121 (9825)
ADT WO 9800013 A1 WO 97-US11280 970627; AU 9735837 A AU 97-35837 970627
FDT AU 9735837 A Based on WO 9800013
PRAI US 96-20849 960628
AN 98-086658 [08] WPIDS
AB WO 9800013 A UPAB: 980223
The following are claimed: (1) killing human **cancer** cells (HCC's) comprising: (a) introducing a nucleic acid encoding human double-stranded RNA dependent **protein kinase** (PKR) to a HCC with an expression system expressing human PKR in the HCC, and (b) contacting the **cancer** cell with tumour necrosis factor (TNF), where nucleic acid encoding human PKR inhibits proliferation of cultured **cancer** cells and the cultured **cancer** cells are grown with a foetal bovine serum (FBS) at 37 deg. C; (2) killing HCC's performed analogically to (1), but where the **cancer** cells are contacted with poly I:C; (3) a composition comprising: (a) a plasmid or a viral vector; (b) a tumour-specific promoter (TSP); (c) a PKR gene operably linked to the TSB and operatively linked to a genome of the viral vector or to the plasmid, and optionally (d) HCC the gene of (c) located inside the HCC, and (4) identifying chemotherapeutic compounds comprising: (a) (1a); (b) contacting the **cancer** cell with at least 1 chemotherapeutic compound, and (c) detecting a difference in the **cancer** cell exposed to the chemotherapeutic compound to a **cancer** cell not exposed to the chemotherapeutic compound, where the **cancer** cell is grown with or without serum and the chemotherapeutic compound is at a concentration of at most 10 mu M.
USE - The methods and composition are used to treat, e.g. colorectal, pancreatic, cervical or lung **cancer** or hepatocarcinoma.
ADVANTAGE - The expression of PKR renders **cancer** cells more prone to develop **apoptosis**. They can provide for targeted **apoptosis** to minimise the likelihood of sudden, massive tumour lysis and inflammatory response.
Dwg.0/9

L144 ANSWER 12 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-051490 [05] WPIDS
CR 96-259065 [26]; 97-153579 [14]; 98-167929 [05]
DNC C98-017542
TI GTPase effector proteins - useful in screening assays for anti

proliferative agents, etc..
DC B04 D16 K08
IN ABO, A; MARTIN, G A
PA (ONYX-N) ONYX PHARM INC
CYC 1
PI US 5698428 A 971216 (9805)* 42 pp
ADT US 5698428 A Cont of US 95-369780 950106, Cont of US 95-475682 950607, US 97-780833 970110
FDT US 5698428 A Cont of US 5518911, Cont of US 5605825
PRAI US 95-369780 950106; US 95-475682 950607; US 97-780833 970110
AN 98-051490 [05] WPIDS
CR 96-259065 [26]; 97-153579 [14]; 98-167929 [05]
AB US 5698428 A UPAB: 980410
Novel **proteins**(referred to as GTPase effector **proteins** or p21-binding **proteins**) that bind to rac1 or CDC42Hs but not to RhoA, are abundant in cytosolic fractions of human neutrophils and HL-60 cells, and have molecular weights of 62, 65 and 68 kD, as determined by SDS-PAGE under reducing conditions. Also claimed are complexes of the **proteins** with a p21 **protein** or GTPase.
USE - The **proteins** can be used in screening assays to identify compounds that modulate their properties, e.g. their **protein kinase** activity, p21-binding activity or p21-induced autophosphorylation activity, where such compounds may be useful as antiproliferative agents for treating **neoplasia**, inflammation, lymphoproliferative conditions, arthritis, autoimmune diseases, **apoptosis**, etc. The **proteins** can also be used to generate phosphorylated **proteins** and amino acids. The complexes can be used to identify agents that modulate phosphate release from such complexes.
Dwg.0/10

L144 ANSWER 13 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-535828 [49] WPIDS
DNC C97-171384
TI **Apoptosis** inducing **protein** ASK1 for treatment of malignant tumours - has **protein kinase** activity and enhances SEK1 and MKK3 **kinase** activity in TNF.
DC B04 D16
IN ICHIJO, H; MIYAZONO, K
PA (NICA-N) JAPAN FOUND CANCER RES; (GANK-N) ZH GAN KENKYUKAI
CYC 21
PI WO 9740143 A1 971030 (9749)* JA 75 pp
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA US
AU 9725763 A 971112 (9811)
JP 10000093 A 980106 (9811) 36 pp
ADT WO 9740143 A1 WO 97-JP1348 970418; AU 9725763 A AU 97-25763 970418; JP 10000093 A JP 96-241063 960823
FDT AU 9725763 A Based on WO 9740143
PRAI JP 96-241063 960823; JP 96-122320 960419
AN 97-535828 [49] WPIDS
AB WO 9740143 A UPAB: 971211
A novel **protein** (ASK1) induces **apoptosis** by enhancing SAPK, JNK and/or p38 activity, and also enhances SEK1 and/or MKK3 activity (e.g. in tumour necrosis factor). The **protein** has **protein kinase** activity. The sequence of human ASK1 is given (1375 amino acids).
USE - The **protein** ASK1 and its derivatives are useful for the treatment of malignant tumours such as Burkett's lymphoma, myeloma,

lung **cancer**, ovarian **cancer**, brain tumours, carcinoma and sarcoma. Gene therapy of tumours using the DNA vector in a suitable viral or other carrier is also possible.
Dwg.0/0

L144 ANSWER 14 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-489642 [45] WPIDS
DNN N97-407814 DNC C97-156126
TI New nucleic acid encoding the TRIO phospho protein - used for diagnosis and treatment of proliferative and neurodegenerative diseases.
DC B04 D16 P14 S03
IN DEBANT, A; SERRA-PAGES, C; STREULI, M
PA (DAND) DANA FARBER CANCER INST INC
CYC 20
PI WO 9735979 A1 971002 (9745)* EN 141 pp
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9725556 A 971017 (9807)
ADT WO 9735979 A1 WO 97-US5236 970327; AU 9725556 A AU 97-25556 970327
FDT AU 9725556 A Based on WO 9735979
PRAI US 96-14214 960327
AN 97-489642 [45] WPIDS
AB WO 9735979 A UPAB: 971113
A novel isolated nucleic acid (I) encodes: (a) TRIO, a phosphoprotein with the 2860 amino acid (aa) sequence given in the specification; or (b) a **protein** with at least 60% (preferably 90%) homology with TRIO and retaining TRIO bioactivity. Also new are: (1) a nucleic acid that: (a) specifically detects a TRIO coding sequence; (b) hybridises under stringent conditions with the 8906 bp TRIO coding sequence given in the specification; (c) encodes a TRIO fusion **protein**; or (d) is antisense to the coding strand of (I); (2) a vector containing (I); (3) a host cell containing the vector of (2); (4) an isolated TRIO **protein** containing a TRIO GEF (guanine nucleotide exchange factor) domain or a TRIO **kinase** domain, and having TRIO bioactivity; (5) a TRIO fusion **protein**; (6) antibodies (Ab) that bind TRIO specifically; and (7) non-human transgenic animals containing cells that include a transgene encoding TRIO or in which the sequence for TRIO is enhanced, induced, disrupted, prevented or suppressed.

USE - The host cells of (3) are cultured to produce recombinant TRIO **protein**, e.g. for Ab production (claimed). Labelled Ab and nucleic acid probes are used to detect/quantify TRIO activity at the **protein** or nucleic acid levels (claimed), particularly for diagnosis and phenotyping of **neoplastic** or hyperplastic disease. The Ab can also be used to screen cDNA libraries, and detection of mutation/modulation of a TRIO-encoding gene, or abnormal expression of this gene, is used to identify cells at risk of transformation. Modulators of TRIO activity (e.g. Ab, antisense nucleic acids, peptides or mimics), are used to reorganise the actin cytoskeleton (claimed), e.g. in cases of wound healing and/or tumour metastasis. The modulators are also used to treat an oncogene (claimed), or more generally to control growth, differentiation, migration and/or survival of cells, e.g. regulation of the immune response to infection, treatment of impaired immune response (as in chronic granulomatous disease), control of **apoptosis** in **cancer** therapy, and treatment of degenerative diseases (e.g. Parkinson's, Alzheimer's or Huntington's, amyotropic lateral sclerosis, gastric ulcers, Wilm's tumour etc.). The TRIO **protein** is used to screen for its modulators. The transgenic animals can be used similarly or as models to characterise TRIO genes and **proteins**.
Dwg.0/10

L144 ANSWER 15 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-425048 [39] WPIDS
DNC C97-136091
TI Inducing **apoptosis** in tumour cells - using combination of antitumour therapeutic agent and modulating agent, particularly **protein kinase** C inhibitors.
DC B04
IN ALBINO, A P; SCHWARTZ, G K
PA (SLOK) SLOAN KETTERING INST CANCER RES
CYC 22
PI WO 9730174 A1 970821 (9739)* EN 226 pp
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP MX US
AU 9721952 A 970902 (9751)
US 5821072 A 981013 (9848)
ADT WO 9730174 A1 WO 97-US3341 970220; AU 9721952 A AU 97-21952 970220; US 5821072 A US 96-603814 960220
FDT AU 9721952 A Based on WO 9730174
PRAI US 96-619304 960321; US 96-603814 960220
AN 97-425048 [39] WPIDS
AB WO 9730174 A UPAB: 970926
Method (A) for screening for a modulating agent (MA) which, when combined with an antitumour therapeutic agent increases **apoptosis** in tumour cells comprises:
(a) contacting tumour cells with the MA and with an antitumour agent known to cause **apoptosis** when used in combination with an appropriate MA to increase **apoptosis** in tumour cells;
(b) determining the degree of **apoptosis** of tumour cells from step (a), and
(c) comparing the degree of **apoptosis** determined in step (b) with the degree of **apoptosis** of tumour cells which are treated with only the antitumour therapeutic agent or only the MA an increase in **apoptosis** indicating that the MA in combination with an antitumour therapeutic agent is capable of increasing **apoptosis** in tumour cells.
USE - The methods can be used for treating tumours such as lymphoma, adenocarcinoma, glioblastoma, leukaemia, oesophageal carcinoma, head and neck **cancer**, prostate **cancer**, lung **cancer**, melanoma, cervical carcinoma, pancreatic **cancer**, sarcoma, hepatoma, gallbladder **cancer**, gastrointestinal **cancer**, breast **cancer** or an ovarian **cancer** (all claimed).
Dwg.0/12

L144 ANSWER 16 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-363452 [33] WPIDS
DNC C97-116454
TI Use of protease(s) other than bromelain - for treating conditions mediated by intracellular signal pathways, e.g. **cancer**, allergies, auto-immune disease or transplant rejection.
DC B04 D16
IN ENGWERDA, C; MYNOTT, T L; MYNOTT, T
PA (CORT-N) CORTECS LTD; (CORT-N) CORTECS UK LTD
CYC 76
PI WO 9724138 A2 970710 (9733)* EN 27 pp
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX

NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
AU 9711818 A 970728 (9746)
WO 9724138 A3 971016 (9815)
ZA 9610433 A 980826 (9840) 28 pp
EP 876153 A2 981111 (9849) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE SI
ADT WO 9724138 A2 WO 96-GB3089 961213; AU 9711818 A AU 97-11818 961213; WO 9724138 A3 WO 96-GB3089 961213; ZA 9610433 A ZA 96-10433 961211; EP 876153 A2 EP 96-942449 961213, WO 96-GB3089 961213
FDT AU 9711818 A Based on WO 9724138; EP 876153 A2 Based on WO 9724138
PRAI GB 95-26691 951229
AN 97-363452 [33] WPIDS
AB WO 9724138 A UPAB: 981021
Protease other than bromelain can be used in the preparation of an agent for: (a) modulating intracellular signal pathways which depend upon inositol phosphates, **protein kinases** and/or **protein** phosphatases; (b) the treatment or control of a disease mediated by inositol phosphate, **protein kinase** and/or **protein** phosphatase-mediated intracellular signal transduction; (c) enhancing the immune system; (d) inhibiting cytokine production; (e) the treatment of **cancer**; (f) use in the prevention or treatment of allergies; (g) preventing **apoptosis**, and (h) use in inhibiting, preventing or treating parasite and/or pathogen infection.
USE - The proteases can be used either to stimulate or to inhibit cytokine production depending on whether they are used to treat activated cells (such as those already receiving stimuli) or inactivated (i.e. quiescent or resting) cells. They can be used as adjuvants for vaccines and for the treatment or prevention of an autoimmune disease or transplant rejection by a host such as toxic shock, diabetes mellitus, multiple sclerosis or rheumatoid arthritis. The proteases can be used in doses of e.g. 50-4000 (preferably 100-1000) GDU/day.
Dwg.0/4

L144 ANSWER 17 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-319721 [29] WPIDS
DNC C97-103256
TI New purine derivatives that inhibit cyclin-dependent kinase(s) - are useful as herbicides and as anti-proliferative agents for treating **cancer**, psoriasis etc..
DC B02 C02
IN BISAGNI, E; LEGRAVEREND, M; MEIJER, L
PA (CNRS) CNRS CENT NAT RECH SCI
CYC 21
PI WO 9720842 A1 970612 (9729)* FR 52 pp
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP US
FR 2741881 A1 970606 (9730) 33 pp
EP 874847 A1 981104 (9848) FR
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9720842 A1 WO 96-FR1905 961129; FR 2741881 A1 FR 95-14237 951201; EP 874847 A1 EP 96-941088 961129, WO 96-FR1905 961129
FDT EP 874847 A1 Based on WO 9720842
PRAI FR 95-14237 951201
AN 97-319721 [29] WPIDS
AB WO 9720842 A UPAB: 970716
Purine derivatives of formula (I) in optically-active or racemic forms and optionally as geometric isomers, having an IC50 at most 5 mu M for cdc2/cyclin B (cdc = catalytic subunit of a cyclin-dependent **protein kinase** (cdk); cyclin = the regulatory subunit)

are new. In (I), R2, R6 and R9 = halo, RNH, RNH-NH, NH2-R'-NH- or RNH-R'-NH-; R = alkyl, aryl, cycloalkyl or heterocyclyl; R' = alkylene, arylene or cycloalkylene; both R and R' have 1-8 C and are optionally substituted by OH, halo, amino or alkyl; R2 may also be heterocyclyl, optionally substituted by R; R9 may also be alkyl, aryl or cycloalkyl; R2 and R9 can also be H but with provisos e.g.(a) R6, R9 = benzylamino and Me; and (b) R2, R6 = 2-hydroxyethylamino and benzylamino.

USE - (I) are anti-proliferative agents useful as anti-mitotic agents. (I) inhibit hyperphosphorylation of tau **protein** by cdk5 and are particularly used for treating **cancer** but also psoriasis, fungal or protozoal infections and Alzheimer's disease (all claimed). Other claimed uses of (I) are as anti-neurodegenerative agents (especially inhibitors of neuronal **apoptosis**) and as herbicides.

ADVANTAGE - (I) reversibly inhibit cdc2, cdk2 and cdk5 at low doses; retain high specificity (specifically they do not inhibit erk 1 and 2) and are not cytotoxic. (I) increase effect of conventional antitumour agents such as taxol, cisplatin, DNA-intercalating agents etc.

Dwg.0/8

L144 ANSWER 18 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-153579 [14] WPIDS
CR 96-259065 [26]; 98-051490 [05]; 98-167929 [05]
DNC C97-049070
TI Human p21-activated serine **kinase** p65 **protein** - useful for screening potential modulators of **neoplasia**, lymphoproliferative conditions, arthritis, inflammation, autoimmune disease, etc..
DC B04 D16
IN ABO, A; MARTIN, G A
PA (ONYX-N) ONYX PHARM INC
CYC 1
PI US 5605825 A 970225 (9714)* 42 pp
ADT US 5605825 A Cont of US 95-369780 950106, US 95-475682 950607
FDT US 5605825 A Cont of US 5518911
PRAI US 95-369780 950106; US 95-475682 950607
AN 97-153579 [14] WPIDS
CR 96-259065 [26]; 98-051490 [05]; 98-167929 [05]
AB US 5605825 A UPAB: 980410

Isolated polypeptides (I) having at least 95% identity to sequences comprising amino acids 1-506, 49-113, 231-486 and 1-481 of the 506 amino acid sequence shown in the specification (seq1) are new. The following are also claimed: (1) an hPAK65 fragment that binds rac1 or CDC42H, esp. where the fragment comprises amino acids 49-113 of seq1 and/or binds an immunoglobulin; (2) an hPAK65 fragment that corresponds to a p21 binding domain, esp. comprising amino acids 49-113 of seq1; and (3) an hPAK65 fragment that corresponds to a **kinase** domain, esp. comprising amino acids 1-481 of seq1. Also claimed are fusion **proteins** comprising a polypeptide (I) joined to a heterologous **protein** (II).

USE - The polypeptides (I) comprise human p21-activated serine **kinase** p65 **protein** (hPAK65) and fragments of hPAK65. The polypeptides are useful for identifying agents that (a) modulate the interaction of hPAK65 with rho-like p21 GTPases, esp. the binding of rac1 and CDC42Hs to hPAK65 and subsequent activation of hPAK65's serine **protein kinase** activity, (b) modulate hPAK65's serine **protein kinase** activity or (c) modulate the effect of hPAK65 on p21 **protein** GTPase. Such agents may be useful for treating **cancer**, lymphoproliferative conditions, arthritis, inflammation, autoimmune diseases, **apoptosis**, etc. The

polypeptides can also be used to generate antibodies for detection of PAK65 and PAK65-complexes.
Dwg.0/10

L144 ANSWER 19 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-077522 [07] WPIDS
DNC C97-024961
TI Mitogen-activated **protein kinase** phosphatase, MKP-2 - used in the control of cell growth, differentiation and **apoptosis**
.
DC B04 D16
IN MISRA-PRESS, A; STORK, P J S
PA (UYOR-N) UNIV OREGON HEALTH SCI
CYC 70
PI WO 9700315 A1 970103 (9707)* EN 67 pp
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
AU 9662811 A 970115 (9718)
ADT WO 9700315 A1 WO 96-US10402 960614; AU 9662811 A AU 96-62811 960614
FDT AU 9662811 A Based on WO 9700315
PRAI US 95-263 950616
AN 97-077522 [07] WPIDS
AB WO 9700315 A UPAB: 970212
An isolated nucleic acid (I) comprising a nucleotide sequence encoding mammalian mitogen-activated **protein kinase** phosphatase-2 (MKP-2) **protein**, is new. Also claimed are: (1) a recombinant vector comprising (I); (2) a transformant host cell transfected with the vector of (1); (3) a **protein** encoded by (I); (4) an antibody capable of binding to the **protein** of (3); and (5) a hybridoma cell line capable of producing the above antibody.
USE - The MKP-2 is used in the control of cell growth, differentiation and **apoptosis**.
ADVANTAGE - Large amts of highly pure **protein** may be produced without resort to the costlier and more time consuming methods involved in purifying the enzymes from tissues.
Dwg.0/23

L144 ANSWER 20 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-012100 [01] WPIDS
DNC C97-003411
TI Receptor interacting **protein** having death and **kinase** domain - useful to control diseases that involve abnormal **apoptosis**, and for diagnosis and drug screening.
DC B04 D16 S03
IN KIM, E; LEDER, P; LEE, T; SEED, B; STRANGER, B Z; STANGER, B Z
PA (GEHO) GEN HOSPITAL CORP; (HARD) HARVARD COLLEGE
CYC 22
PI WO 9636730 A1 961121 (9701)* EN 64 pp
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9654873 A 961129 (9712)
US 5674734 A 971007 (9746) 24 pp
EP 852627 A1 980715 (9832) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
ADT WO 9636730 A1 WO 96-US5386 960418; AU 9654873 A AU 96-54873 960418; US 5674734 A US 95-444005 950518; EP 852627 A1 EP 96-911803 960418, WO

96-US5386 960418
FDT AU 9654873 A Based on WO 9636730; EP 852627 A1 Based on WO 9636730
PRAI US 95-444005 950518
AN 97-012100 [01] WPIDS
AB WO 9636730 A UPAB: 970102
Novel isolated receptor interacting **protein** (RIP): (a) comprises a death domain in its C-terminal region; (b) comprises a **kinase** domain in its N-terminal region; (c) interacts with a Fas/APO-1 intercellular domain; and (d) induces **apoptosis** in eukaryotic cells.
USE - Specific inhibition of **apoptosis**, i.e. RIP binding inhibition, can be used to treat, e.g. neurodegeneration, aplastic anaemia, ischaemia, toxin-induced liver disease etc., while stimulation of **apoptosis** can be used to treat **cancer**, autoimmune disease, viral infections, etc.. Cells that can be induced to undergo **apoptosis** can be used in gene therapy, i.e. RIP can be used to control the number of cells bearing a partic. gene, or to act as an antitumour agent in treatments that depend on the delivery of a lethal gene to **neoplastic** cells. The Ab and RIP are useful as diagnostic and research reagents, e.g. in the new screening assays, and the Ab is also useful for RIP affinity purificn..
ADVANTAGE - RIP kills both mitotically active and inactive **cancer** cells, and avoids the need to generate toxic agents in the cells, in contrast to known chemotherapeutic and gene therapy agents.
Dwg.0/4
ABEQ US 5674734 A UPAB: 971119
An isolated DNA molecule fragment comprising a nucleotide sequence encoding a receptor interacting protein (RIP) whose amino acid sequence is selected from the group consisting of SEQ ID NO:15 (656 amino acids) and amino acids 1-671 of SEQ ID NO:17 (671 amino acids).
Dwg.0/4

L144 ANSWER 21 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 96-259065 [26] WPIDS
CR 97-153579 [14]; 98-051490 [05]; 98-167929 [05]
DNC C96-081968
TI Human serine **protein kinase** p65 and related nucleic acid - useful in screening modulators, potentially useful in treatment of **cancer**, arthritis etc..
DC B04 D16
IN ABO, A; MARTIN, G A
PA (ONYX-N) ONYX PHARM INC
CYC 21
PI US 5518911 A 960521 (9626)* 42 pp
WO 9620948 A1 960711 (9633) EN 116 pp
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9647560 A 960724 (9644)
EP 802921 A1 971029 (9748) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
ADT US 5518911 A US 95-369780 950106; WO 9620948 A1 WO 96-US487 960105; AU 9647560 A AU 96-47560 960105; EP 802921 A1 EP 96-903482 960105, WO 96-US487 960105
FDT AU 9647560 A Based on WO 9620948; EP 802921 A1 Based on WO 9620948
PRAI US 95-369780 950106
AN 96-259065 [26] WPIDS
CR 97-153579 [14]; 98-051490 [05]; 98-167929 [05]
AB US 5518911 A UPAB: 980410
A purified, isolated nucleic acid (I), comprising a 2248 bp sequence given

in the specification and encoding human PAK (**protein** activated serine **kinase**) 65 **protein** (A, 506 amino acid (aa) sequence reproduced) and able to hybridise to hPAK65 nucleic acid under highly stringent conditions, is new. Also new are (1) vectors contg. (I); and (2) host cells transformed with (I).

USE - The transformed cells are able to express (A) with constitutive serine **kinase** activity. (A) is useful for screening cpds. for the ability to modulate hPAK65 activity (partic. its interaction with rho-like p21 GTPases), i.e. to identify potential therapeutic agents for **neoplasia**, lymphoproliferation, arthritis, angiogenesis, inflammation, autoimmune disease and **apoptosis**. It can also be used to produce antibodies for detecting or isolating PAK65 and its complexes. (I), or its fragments, can be used in antisense therapy, and as probes or primers for isolating homologous sequences.

Dwg.0/10

L144 ANSWER 22 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 96-151333 [15] WPIDS
DNC C96-047540
TI Immuno-conjugate comprising **tyrosine kinase** inhibitor linked to antibody - binds to cell surface receptor of cell with **tyrosine kinase** activity, used to induce **apoptosis** in target cells, and to treat, e.g. **cancers** and auto-immune diseases.
DC B04 D16
IN UCKUN, F M
PA (MINU) UNIV MINNESOTA
CYC 65
PI WO 9606116 A1 960229 (9615)* EN 59 pp
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TT UA UG UZ VN
AU 9532168 A 960314 (9625)
US 5587459 A 961224 (9706) 34 pp
EP 776338 A1 970604 (9727) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 10505056 W 980519 (9830) 62 pp
EP 776338 B1 981209 (9902) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9606116 A1 WO 95-US10123 950808; AU 9532168 A AU 95-32168 950808; US 5587459 A US 94-293731 940819; EP 776338 A1 EP 95-928368 950808, WO 95-US10123 950808; JP 10505056 W WO 95-US10123 950808, JP 96-508124 950808; EP 776338 B1 EP 95-928368 950808, WO 95-US10123 950808
FDT AU 9532168 A Based on WO 9606116; EP 776338 A1 Based on WO 9606116; JP 10505056 W Based on WO 9606116; EP 776338 B1 Based on WO 9606116
PRAI US 94-293731 940819
AN 96-151333 [15] WPIDS
AB WO 9606116 A UPAB: 960417
Immunoconjugate comprises a **tyrosine kinase** (TK) inhibitor linked to an antibody which binds to a cell surface receptor of a cell with TK activity, and inhibits the receptor-associated TK of the cell without directly affecting other cell's TK.

USE - The inhibitors induce **apoptosis** in target cells. The antibodies are specific to receptors on **cancer** cells. The immuno-conjugates kill in vitro the clonogenic fragments of target tumour cells, can penetrate multiple organs in the SCID mouse model, and selectively accumulate in those organs infiltrated with human tumour cells. They may also be useful as immunosuppressive agents to suppress

T-cell proliferation associated with organ rejection, or to treat autoimmune diseases.

ADVANTAGE - The immuno-conjugates can also kill in vivo therapy-refractory human leukaemia cells without any toxicity in a surrogate model of human leukaemia, and are superior to the antibody of TK inhibitors used alone, and to all other drugs used in model systems.

Dwg.0/10

ABEQ US 5587459 A UPAB: 970205

An immunoconjugate comprising genistein linked to an anti-CD19 antibody which specifically binds to cell surface CD19 receptor, wherein said immunoconjugate inhibits CD19 associated **tyrosine kinase**, thereby inducing **apoptosis** and cell death.

Dwg.0/10

L144 ANSWER 23 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 96-105851 [11] WPIDS
DNC C96-033510
TI Oligo nucleoside cpds to inhibit focal adhesion **kinase** **protein** in animals - comprise modified linkages, esp. used to treat **cancer**..
DC B04
IN CANCE, W G; LIU, E T; OWENS, L V
PA (UYNC-N) UNIV NORTH CAROLINA
CYC 24
PI WO 9602560 A1 960201 (9611)* EN 71 pp
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP KR MX NZ US
AU 9531336 A 960216 (9622)
EP 772625 A1 970514 (9724) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 10502820 W 980317 (9821) 71 pp
ADT WO 9602560 A1 WO 95-US9040 950718; AU 9531336 A AU 95-31336 950718; EP 772625 A1 EP 95-927246 950718, WO 95-US9040 950718; JP 10502820 W WO 95-US9040 950718, JP 96-505236 950718
FDT AU 9531336 A Based on WO 9602560; EP 772625 A1 Based on WO 9602560; JP 10502820 W Based on WO 9602560
PRAI US 94-276843 940718
AN 96-105851 [11] WPIDS
AB WO 9602560 A UPAB: 960315

An oligonucleotide (ON) cpd (I) for inhibiting expression of a focal adhesion **kinase** (FAK) **protein** comprises 6-40 linked nucleosides in a sequence that is complementary to a target region of a FAK mRNA. Also claimed is a formulation comprising (I) and a vehicle adapted to allow delivery of (I) to animal cells.

USE - (I) are used in methods to inhibit growth and invasiveness of a transformed animal cell and to inhibiting cell colony formation. It may also be used for inducing **apoptosis** and for reducing the rate of tumour formation attributable to transformed cells (claimed). (I) are also used to treat **cancer**.

ADVANTAGE - (I) are effective in inhibiting the expression of FAK **protein** product in transformed (i.e. **cancerous**) human cells, and such inhibition results in reduced **cancer** cell growth and adhesion, induction of cell **apoptosis**, reduced cell motility and invasiveness reduced cell colony formation and anchorage independent cell growth, and reduced rates of tumour formation.

Dwg.0/13

L144 ANSWER 24 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 96-068708 [07] WPIDS

DNC C96-022331
TI Use of bromelain to prepare medicaments - for treating diseases mediated by intracellular signal transduction e.g. **cancer**, allergies, toxic shock etc..
DC B04
IN ENGWERDA, C; MYNOTT, T L; MYNOTT, T
PA (CORT-N) CORTECS LTD
CYC 66
PI WO 9600082 A1 960104 (9607)* EN 69 pp
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TT UA UG US UZ VN
AU 9527493 A 960119 (9616)
NO 9605564 A 970224 (9718)
EP 766565 A1 970409 (9719) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
FI 9605204 A 970221 (9721)
ZA 9505292 A 970923 (9744) 66 pp
JP 10502073 W 980224 (9818) 61 pp
KR 97703784 A 970809 (9836)
ADT WO 9600082 A1 WO 95-GB1501 950626; AU 9527493 A AU 95-27493 950626; NO 9605564 A WO 95-GB1501 950626, NO 96-5564 961223; EP 766565 A1 EP 95-922672 950626, WO 95-GB1501 950626; FI 9605204 A WO 95-GB1501 950626, FI 96-5204 961223; ZA 9505292 A ZA 95-5292 950626; JP 10502073 W WO 95-GB1501 950626, JP 96-502932 950626; KR 97703784 A WO 95-GB1501 950626, KR 96-707424 961224
FDT AU 9527493 A Based on WO 9600082; EP 766565 A1 Based on WO 9600082; JP 10502073 W Based on WO 9600082; KR 97703784 A Based on WO 9600082
PRAI GB 94-12711 940624
AN 96-068708 [07] WPIDS
AB WO 9600082 A UPAB: 960222
Use of bromelain (I) in prepn. of agents for following purposes is claimed: (1) for modulating intracellular signal pathways that depend on inositol phosphates, **protein kinases** and/or **protein** phosphatases; (2) for treatment or control of disease mediated by intracellular signal transduction mediated by inositol phosphates, **protein kinases** and/or **protein** phosphatases; (3) for modulating cytokine prodn.; (4) for treatment or prevention of autoimmune disease or transplant rejection; (5) for preventing or treating toxic shock; (6) for use as vaccine adjuvant; (7) for treatment of **cancer**; (8) for prevention or treatment of allergies; (9) for preventing **apoptosis**; and (10) for inhibiting, preventing or treating parasite and/or pathogen infection.
ADVANTAGE - Bromelain, a mixt. of enzymes derived from pineapple stem, is a modular of intracellular signal transduction partic. a modulator of pathways involving inositol phosphates. The daily dose may be 50-4000 (e.g. 100-1000) gelatin digestion units (GDU). An esp. pref. dose is 10 mg/kg.
Dwg.0/15

L144 ANSWER 25 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 95-275290 [36] WPIDS
DNC C95-124819
TI Inhibiting lymphocyte proliferation with transition metal complexes - esp. of vanadium, tungsten and molybdenum complexed with oxo and peroxo gps.; useful for treating leukaemia or lymphoma(s).
DC B05
IN SCHIEVEN, G L

PA (BRIM) BRISTOL-MYERS SQUIBB CO
CYC 21
PI WO 9520390 A1 950803 (9536)* EN 166 pp
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: CA JP MX US
EP 735880 A1 961009 (9645) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
US 5565491 A 961015 (9647) 36 pp
US 5583242 A 961210 (9704) 29 pp
JP 09508392 W 970826 (9744) 141 pp
US 5693627 A 971202 (9803) 31 pp
MX 9603094 A1 970301 (9820)
US 5846998 A 981208 (9905)
ADT WO 9520390 A1 WO 95-US1234 950130; EP 735880 A1 EP 95-909397 950130, WO 95-US1234 950130; US 5565491 A US 94-189330 940131; US 5583242 A Div ex US 94-189330 940131, US 95-450342 950525; JP 09508392 W JP 95-520240 950130, WO 95-US1234 950130; US 5693627 A Div ex US 94-189330 940131, US 95-450401 950525; MX 9603094 A1 MX 96-3094 960730; US 5846998 A CIP of US 94-189330 940131, WO 95-US1234 950130, US 96-669499 960618
FDT EP 735880 A1 Based on WO 9520390; JP 09508392 W Based on WO 9520390; US 5693627 A Div ex US 5565491; US 5846998 A CIP of US 5565491, Based on WO 9520390
PRAI US 94-189330 940131; US 95-450342 950525; US 95-450401 950525; US 96-669499 960618
AN 95-275290 [36] WPIDS
AB WO 9520390 A UPAB: 950918
Proliferation of T cells, B cells or their malignantly transformed derivs. is inhibited by treatment with a coordinate covalent complex (CCC) comprising: (i) a metal ion selected from Mo(VI), W(VI), or V (V) ion; (ii) an oxo gp. covalently bonded to the metal ion; (iii) opt. 1 peroxo gp. coordinate-covalently bonded to the metal ion; and (iv) 1 organic moiety (I) coordinate-covalently bound to the metal through 1 N-or O-contg. functional gp. able to donate electrons to the coordinate-covalent bond. (CCC) has sufficient affinity for the active site of phosphotyrosine phosphatase (PTP) to inhibit the activity of this enzyme. In a variant, (I) is boned through an N, O or As contg. gp. able to donate electrons and (CCC) contains 1 or 2 peroxo gps. occupying 2 sites in the coordination sphere of the metal ion. (CCC) are new cpds. where: (a) the metal ion is not V(V); and (b) the complex has affinity for the PTP active site to that of bis(maltolato)oxovanadium (IV) (BMLOV).

USE - The CCC are used to treat leukaemia or lymphoma (derived from opt. transformed T or B cells or myeloid cells), partic. in conjunction with ionising radiation, where a synergistic effect is achieved and **apoptosis** is induced. They can also be used to prevent class-switching of antibody producing cells to reduce IgE formation (treatment of allergy), and to induce **tyrosine** phosphorylation in (transformed) T and B cells (as a result of PTP inhibition and/or **tyrosine kinase** activation). The CCC can be used to suppress growth of tumour cells overexpressing a **tyrosine kinase** (esp. HER1-4 or Src) or requiring PTP for growth and/or survival, opt. in conjunction with a therapeutic agent and to activate **tyrosine kinases** of the 352/60 family (all claimed).
Further uses include control of B cell proliferation to treat autoimmune disease and transplant rejection, treatment of protozoal infection, studies on B cells to determine susceptibility to radiation and chemicals etc., and purging of bone marrow for autologous transplants. The CCC are admin. to provide 1-100 muM in the blood and/or tissue, partic. given orally or by injection.

ADVANTAGE - Treatment with (A) is specific for lymphocytes and does

not induce neutropaenia (A) are active against some tumours resistant to other drugs.
Dwg.17/21

ABEQ US 5565491 A UPAB: 961124
A method for inhibiting B cell proliferation comprises the step of contacting proliferating B cells with a compound comprising a metal selected from the group consisting of vanadium (IV), copper (II) and gallium (II) coordinate-covalently bound to an organic moiety selected from the group consisting of: (a) keto-enol tautomers with the keto and enol groups on adjacent carbon atoms that form 5-membered rings including the metal; and (b) beta diketones in which the two keto groups are separated by one carbon atom, that form a 6-membered ring including the metal, the compound inhibiting phosphotyrosine phosphatase and being administered in a quantity sufficient to detectably inhibit proliferation as measured by incorporation of nucleotides into DNA.
Dwg.0/11

ABEQ US 5583242 A UPAB: 970122
Vanadyl 2-acetyl-1-tetralone.

A metal-organic covalent compound comprising vanadium (IV) coordinate-covalently bound to an organic moiety that is a keto-enol tautomer with the keto and enol groups on adjacent carbon atoms and that forms a 5-membered ring including the metal, the organic moiety being selected from the group consisting of 2-hydroxy-2,4,6-cycloheptatrien-1-one, 3-bromo-2-hydroxy-2,4,6-cycloheptatrien-1-one, 3-hydroxy-1,2-dimethyl-4(1H)-pyridone, 3-ethyl-2-hydroxy-2-cyclopenten-1-one, 3,4-dihydroxy-3-cyclobuten-1,2-dione, ethyl 2-hydroxy-4-oxo-2-pentenone, 2,3,5,6-tetrahydroxy-1,4-benzoquinone, 2',4'-dihydroxy-2-methoxyacetophenone, 4-hydroxy-5-methyl-4-cyclopenten-1,3-dione, 2-chloro-3-hydroxy-1,4-naphthoquinone, 2-(4-bromophenyl)-3-hydroxymaleimide, 2-hydroxy-3-methyl-2-cyclopenten-1-one, 2',3',4'-trihydroxyacetophenone, furoin, 2-hydroxy-2-methylpropiophenone, maclurin, alpha-acetyl-4-hydroxy-beta-(hydroxymethyl)-3-methoxycinnamic acid gamma-lactone, 4-hydroxy-5-phenyl-4-cyclopenten-1,3-dione, 1-(4,5-dimethoxy-2-hydroxyphenyl)-3-methyl-2-buten-1-one, purpurogallin, 2,3-dihydroxy-1,4-phenazinedione, alizarin orange, 1-hydroxy-1-methylnaphthalen-2(1H)-one, alizarin, 1,2,7-trihydroxyanthraquinone, fisetin, 3-oxo-4,5,6-trihydroxy-3(H)-xanthene-9-propionic acid, benzoin, 4'-chlorobenzoin, quercetin, morin, myricetin, and 4,4'-dimethylbenzoin.
Dwg.0/11

ABEQ US 5693627 A UPAB: 980119
Proliferation of T cells, B cells or their malignantly transformed derivs. is inhibited by treatment with a coordinate covalent complex (CCC) comprising: (i) a metal ion selected from Mo(VI), W(VI), or V (V) ion; (ii) an oxo gp. covalently bonded to the metal ion; (iii) opt. at least 1 peroxo gp. coordinate-covalently bonded to the metal ion; and (iv) at least 1 organic moiety (I) coordinate-covalently bound to the metal through at least 1 N-or O-contg. functional gp. able to donate electrons to the coordinate-covalent bond. (CCC) has sufficient affinity for the active site of phosphotyrosine phosphatase (PTP) to inhibit the activity of this enzyme. In a variant, (I) is boned through an N, O or As contg. gp. able to donate electrons and (CCC) contains 1 or 2 peroxo gps. occupying 2 sites in the coordination sphere of the metal ion. (CCC) are new cpds. where: (a) the metal ion is not V(V); and (b) the complex has affinity for the PTP active site at least to that of bis(maltolato)oxovanadium (IV) (BMLOV).

USE - The CCC are used to treat leukaemia or lymphoma (derived from opt. transformed T or B cells or myeloid cells), partic. in conjunction with ionising radiation, where a synergistic effect is achieved and **apoptosis** is induced. They can also be used to prevent

class-switching of antibody producing cells to reduce IgE formation (treatment of allergy), and to induce **tyrosine** phosphorylation in (transformed) T and B cells (as a result of PTP inhibition and/or **tyrosine kinase** activation). The CCC can be used to suppress growth of tumour cells overexpressing a **tyrosine kinase** (esp. HER1-4 or Src) or requiring PTP for growth and/or survival, opt. in conjunction with a therapeutic agent and to activate **tyrosine kinases** of the 352/60 family (all claimed).
Further uses include control of B cell proliferation to treat autoimmune disease and transplant rejection, treatment of protozoal infection, studies on B cells to determine susceptibility to radiation and chemicals etc., and purging of bone marrow for autologous transplants. The CCC are admin. to provide 1-100 mu M in the blood and/or tissue, partic. given orally or by injection.

ADVANTAGE - Treatment with (A) is specific for lymphocytes and does not induce neutropaenia (A) are active against some tumours resistant to other drugs.
Dwg.0/11

L144 ANSWER 26 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 95-194030 [25] WPIDS
DNC C95-089782
TI Nucleic acid encoding Bcl-2-associated proteins - used to develop prods. for modulating **apoptosis** in cells for the treatment of e.g. neurodegenerative disease or **cancer**..
DC B04 D16
IN REED, J C; SATO, T; TAKAYAMA, S
PA (LJOL-N) LA JOLLA CANCER RES FOUND
CYC 58
PI WO 9513292 A1 950518 (9525)* EN 73 pp
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ
W: AM AU BB BG BR BY CA CN CZ FI GE HU JP KE KG KP KR KZ LK LT LV MD MG MN MW NO NZ PL RO RU SD SI SK TJ TT UA UZ VN
AU 9511742 A 950529 (9537)
US 5539094 A 960723 (9635) 18 pp
EP 742793 A1 961120 (9651) EN
R: CH DE FR GB IT LI NL
US 5641866 A 970624 (9731) 18 pp
US 5650491 A 970722 (9735) 18 pp
JP 09509304 W 970922 (9748) 72 pp
US 5686595 A 971111 (9751) 18 pp
AU 687952 B 980305 (9820)
ADT WO 9513292 A1 WO 94-US12904 941109; AU 9511742 A AU 95-11742 941109; US 5539094 A US 93-152485 931112; EP 742793 A1 WO 94-US12904 941109, EP 95-902489 941109; US 5641866 A Div ex US 93-152485 931112, US 95-463089 950605; US 5650491 A Div ex US 93-152485 931112, US 95-461360 950605; JP 09509304 W WO 94-US12904 941109, JP 95-513974 941109; US 5686595 A Div ex US 93-152485 931112, US 95-461359 950605; AU 687952 B AU 95-11742 941109
FDT AU 9511742 A Based on WO 9513292; EP 742793 A1 Based on WO 9513292; US 5641866 A Div ex US 5539094; US 5650491 A Div ex US 5539094; JP 09509304 W Based on WO 9513292; US 5686595 A Div ex US 5539094; AU 687952 B Previous Publ. AU 9511742, Based on WO 9513292
PRAI US 93-152485 931112; US 95-463089 950605; US 95-461360 950605; US 95-461359 950605
AN 95-194030 [25] WPIDS
AB WO 9513292 A UPAB: 950630
A nucleic acid molecule is claimed comprising the Bcl-2-associated athanogene-1- (bag-1) which encodes a polypeptide or an active fragment which binds to a Bcl-2-related **protein**. Also claimed are: (1) a

probe comprising a nucleotide sequence that hybridises under relatively stringent hybridisation conditions to the nucleic acid molecule above; (2) a nucleic acid molecule comprising a nucleotide sequence encoding a Bcl-2-associated **protein** (BAP), or an active fragment which binds to a Bcl-2-related **protein**, where the BAP is not an antibody, a Bcl-2-related **protein**, a Raf-related **protein** or a Raf **kinase**; (3) a polypeptide comprising a BAP or an active fragment which binds to a Bcl-2-related **protein**, where the BAP is not an antibody, a Bcl-2-related **protein**, a Raf-related **protein** or a Raf **kinase**; (4) an antibody that specifically binds BAG-1 or a peptide portion of it.

USE - The prods. can be used for detecting agents that can decrease or inhibit binding of a BAP to a Bcl-2-related **protein**, or agents that can induce the dissociation of a bound complex of a BAP and a Bcl-2-related **protein** (claimed). A nucleic acid encoding BAP can be introduced into a cell to increase the ability of a cell to survive, and antisense sequences can be introduced to decrease the ability of a cell to survive (claimed). The prods. can be used to modulate **apoptosis** in the treatment of e.g. neurodegenerative diseases or **cancers**.

Dwg.0/11

ABEQ US 5539094 A UPAB: 960905
A nucleic acid molecule comprising a nucleotide sequence which encodes the human BCL-2-associated protein-1 (BAP-1) with the 189 residue amino acid sequence given in the specification, is new.
Dwg.0/7

ABEQ US 5641866 A UPAB: 970731
An antibody which specifically binds to a Bcl-2 associated protein-1 having the sequence of 219 amino acids or the sequence of 189 amino acids shown in the specification is claimed.
Dwg.0/7

ABEQ US 5650491 A UPAB: 970828
A Bcl-2 associated protein, comprising an amino acid sequence selected from the 219 or 189 amino acids sequences given in the specification is new.
Dwg.0/7

ABEQ US 5686595 A UPAB: 971222
A nucleic acid molecule having a nucleotide sequence selected from a 1054 or 733 bp sequence given in the specification is new.
Dwg.0/7

L144 ANSWER 27 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 94-279762 [34] WPIDS
DNC C94-127736
TI Identifying anti-proliferative peptide(s) which specifically bind to immunoglobulin super-family species idiotype - esp. to inhibit B-cell lymphoma and leukocytic leukaemia cell proliferation, for anti-idiotype therapy.
DC B04 D16
IN BHATT, R R; DOWER, W J; LEVY, R; RENSCHLER, M F
PA (AFFY-N) AFFYMAX TECHNOLOGIES NV; (STRD) UNIV LELAND STANFORD JUNIOR; (BHAT-I) BHATT R R; (DOWE-I) DOWER W J; (LEVY-I) LEVY R; (RENS-I) RENSCHLER M F
CYC 20
PI WO 9418345 A1 940818 (9434)* EN 69 pp
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9461711 A 940829 (9501)
US 5512435 A 960430 (9623) 31 pp

ADT WO 9418345 A1 WO 94-US1319 940204; AU 9461711 A AU 94-61711 940204, WO 94-US1319 940204; US 5512435 A US 93-14426 930205
FDT AU 9461711 A Based on WO 9418345
PRAI US 93-14426 930205; US 93-153341 931115
AN 94-279762 [34] WPIDS
AB WO 9418345 A UPAB: 941013
Antiproliferative peptides are identified by (i) obtaining from a patient, a predetermined cell population comprising cells which express on their extracellular surface an immunoglobulin superfamily species (IgSS) having a single idiotype characteristic to the cell population; (ii) contacting under aq. binding conditions the IgSS to a peptide library comprising members having distinct peptide sequences; (iii) identifying a peptide library member that specifically binds to the IgSS idiotype as an anti-idiotype peptide (A); (iv) contacting (A) to the predetermined cell population under growth conditions and measuring an indicator of cell proliferation or activation in the population; and (v) identifying an (A) which inhibits cell proliferation of the predetermined cell population as an antiproliferative peptide (A1). Opt. the aminoacid sequence of this (A1) is determined.

USE/ADVANTAGE - Non-immunoglobulin antiproliferative peptides which specifically bind to an IgSS idiotype present on lymphoma cells or lymphocytic leukaemia cells are useful for inhibiting the proliferation of such cells (claimed). Thus, a lymphoma or lymphocytic leukaemia can be treated using the peptides (claimed) which includes clonal energy, modulate **tyrosine kinase** activity and/or induce **apoptosis** in cultured cells of the individual B-cell lymphoma. The peptides can be used individually, as complexes of crosslinked peptides or can be conjugated to deliver toxins or radionuclides to **neoplastic** cells bearing the specific IgSS.

Dwg.0/6

ABEQ US 5512435 A UPAB: 960610
A new method for identifying antiproliferative peptides, comprising the steps of:

i) obtaining a predetermined cell population from a patient, wherein said predetermined cell population comprises cells expressing on their extracellular surface an immunoglobulin superfamily species having a single idiotype characteristic to the predetermined cell population;

ii) contacting under aqueous binding conditions said immunoglobulin superfamily species to a peptide library comprising a multiplicity of peptide library members having distinct peptide sequences;

iii) identifying a peptide library member that binds specifically to said immunoglobulin superfamily species idiotype as an anti-idiotype peptide;

iv) contacting under growth conditions said anti-idiotype peptide to said predetermined cell population or their clonal progeny and measuring an indicator of cell proliferation or activation in the predetermined cell population; and

v) identifying an anti-idiotype peptide which inhibits cell proliferation of the predetermined cell population as an antiproliferative peptide.

Dwg.0/3

L144 ANSWER 28 OF 28 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 94-242249 [30] WPIDS
DNC C94-110630
TI New ellipticine derivs. - inhibit **protein** linked **kinases** and are antitumour agents.
DC B02
IN HARADA, N; ODA, K; OHASHI, M; OZAKI, K; TSUJIHARA, K; GENTA, N; OSAKI, K

PA (TANA) TANABE SEIYAKU CO
CYC 26
PI EP 608876 A1 940803 (9430)* EN 27 pp
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
AU 9453947 A 940804 (9433)
CA 2114468 A 940730 (9436)
FI 9400403 A 940730 (9437)
JP 06279441 A 941004 (9444) 26 pp
AU 666416 B 960208 (9613)
TW 269688 A 960201 (9617)
US 5565569 A 961015 (9647) 16 pp
US 5605904 A 970225 (9714) 17 pp
CN 1099034 A 950222 (9722)
SG 42916 A1 971017 (9751)
IL 108461 A 980924 (9844)
JP 2820881 B2 981105 (9849) 25 pp
ADT EP 608876 A1 EP 94-101193 940127; AU 9453947 A AU 94-53947 940124; CA 2114468 A CA 94-2114468 940128; FI 9400403 A FI 94-403 940127; JP 06279441 A JP 94-7016 940126; AU 666416 B AU 94-53947 940124; TW 269688 A TW 94-100620 940125; US 5565569 A US 94-186016 940125; US 5605904 A Div ex US 94-186016 940125, US 95-449273 950524; CN 1099034 A CN 94-101690 940129; SG 42916 A1 SG 96-668 940127; IL 108461 A IL 94-108461 940128; JP 2820881 B2 JP 94-7016 940126
FDT AU 666416 B Previous Publ. AU 9453947; US 5605904 A Div ex US 5565569; JP 2820881 B2 Previous Publ. JP 06279441
PRAI JP 93-13441 930129
AN 94-242249 [30] WPIDS
AB EP 608876 A UPAB: 940914
Ellipticine derivs. of formula (I) and their salts are new: R is substd. lower alkyl, opt. substd. lower alkoxy or a heteromonocyclic gp..
R is lower alkyl (substd. by 1-3 B or opt. substd. Ph), lower alkoxy opt. substd. by 1-3 B or heteromonocycle contg. 1-3 N and/or S; B is opt. substd. lower alkoxy, opt. protected COOH, opt. substd. loweralkoxycarbonyl, opt. substd. phenyl, opt. protected aminocarbonyl, opt. protected amino, opt. protected amino-substd. lower alkanoylamino or opt. protected OH; pref. R is lower alkyl substd. by COOH; lower is 1-6.
USE/ADVANTAGE - (I) have excellent antitumour activity and are used to treat tumours in warm blooded animals. They inhibit p53 **protein** -linked **kinases** i.e. DNA activated **kinase**, casein **kinase** and cdc2 **kinase** causing a specific inhibition of p53 **protein** phosphorylation followed by induction of **apoptosis** of **cancer** cells in which mutant p53 is overexpressed. (I) have high water solubility and show less side effects on circulatory system, e.g. pulsus frequens and low toxicity.
Dwg.0/0
ABEQ US 5565569 A UPAB: 961124
Ellipticine cpd. of formula (I) or pharmaceutically-acceptable salts are new. In (I), R is lower alkyl (opt. substd. by COOH, lower alkoxycarbonyl, lower alkoxy-substd. lower alkoxycarbonyl or carboxyl-substd. lower alkoxycarbonyl.
Dwg.0/0
ABEQ US 5605904 A UPAB: 970407
A method of treating a tumour susceptible to treatment by ellipticine in a warm-blooded animal which comprises administering to said warm-blooded animal a pharmaceutically effective amount of a compound of the formula (I) wherein R is a lower alkyl group substituted by 1 to 3 groups selected from a lower alkoxy group, a lower alkoxy-substituted lower alkoxy group, a carboxyl-substituted lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower alkoxy-substituted lower alkoxycarbonyl

group, a carboxyl-substituted lower alkoxycarbonyl group, an aminocarbonyl group, a lower alkylaminocarbonyl group, an amino group, a lower alkylamino group, a formylamine group, an amino-substituted lower alkanoylamino group, and a hydroxy group; a lower alkoxy group; a lower alkoxy-substituted lower alkoxy group; or a thiazolidinyl group, or a pharmaceutically acceptable salt thereof.
Dwg.0/0